REVIEW

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Eicosanoid regulation of pulmonary innate immunity post-hematopoietic stem cell transplantation

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Abstract

Hematopoietic stem cell transplantation (HSCT) is a therapeutic option for a number of malignant and inherited disorders. However, the efficacy of this therapy is limited by a number of serious infectious and noninfectious complications. Pulmonary infections represent a significant cause of morbidity and mortality post-HSCT and can occur both pre- and post-hematopoietic reconstitution. Susceptibility to Gram-negative bacterial infections despite full hematopoietic engraftment suggests that innate immunity remains impaired months to years post-HSCT. This review will describe the process and complications of HSCT and will summarize what is known about innate immune reconstitution post-HSCT. Data from the literature as well as our own laboratory will be presented to suggest that an eicosanoid imbalance characterized by over-production of prostaglandins and under-production of leukotrienes leads to impaired lung phagocyte function post-HSCT. Of therapeutic interest, strategies which limit production of prostaglandins can improve pulmonary host defense in animal HSCT models, which suggests that this may also be beneficial for human HSCT recipients.

Key words: transplantation, macrophages, neutrophils, innate immunity, eicosanoids, prostaglandins, leukotrienes.

Abbreviations: AA – arachidonic acid, AM – alveolar macrophage, APC – antigen-presenting cell, BM – bone marrow, BO – Bronchiolitis obliterans, COX – cyclooxygenase, cys-LTs – cysteinyl LTs, EP – E prostanoid, EPAC-1 – guanine exchange protein activated by adenyl cyclase, GVHD – graft-versus-host disease, HLA – human leukocyte antigen, HSCT – hematopoietic stem cell transplantation, IPS – idiopathic pneumonia syndrome, LTs – leukotrienes, 5-LO – 5-lipoxygenase, FLAP – 5-LO activating protein, LTB_4 – leukotriene B_4, MHC – major histocompatability complex, PAMPs – pathogen-associated molecular patterns, PLA_2 – phospholipase A_2, PMN – polymorphonuclear leukocyte or neutrophil, TBI – total body irradiation, TLRs – Toll-like receptors.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) has evolved as a therapeutic option for a variety of malignant and inherited diseases, including hematologic cancers, autoimmune deficiencies, and rescue therapy following irradiation for solid tumors [26]. Despite the increased use of HSCT, there are still a number of serious challenges, especially pulmonary complications, which limit the success of this therapy. This review will highlight the various types of HSCT and pulmonary complications (especially infections) occurring post--HSCT. Experimental evidence will also be presented which suggests that pulmonary innate immunity is impaired post-transplant. Finally, we will review the evidence that eicosanoid imbalances post-HSCT contribute to impaired lung host defense.

STEM CELL SOURCE

Stem cells can be collected from numerous sources in the body to be used in HSCT (see Table 1) [26, 51]. The first source of stem cells for transplantation was from the bone marrow (BM). However, the procedure to harvest BM is associated with moderate pain and discomfort for the donor [26]. More recently, stem cells have been purified from the peripheral blood with far less discomfort [26, 87]. Stem cells are identified by expression of the CD34 marker, and the number of these cells in the blood can be increased by mobilizing them with cytokines such as granulocyte colony-stimulating-factor alone or in combination with drugs such as AMD3100, a CXCR4 receptor antagonist which appears to release stem cells from the BM and cause them to enter the circulation [36]. Finally, in situations where the transplant is urgent or suitable donors are not

Table 1. Sources of stem cells for HSCT

Clinical	Bone Marrow Mobilized peripheral blood Cord blood
Animal research	All of the above plus: Fetal liver Embryonic stem cells

found, umbilical cord blood from unrelated donors has been used as a source of hematopoietic stem cells. Of note, both hematologic and immunologic reconstitution is slower in transplants with cord blood; but the advantage is that the histocompatability matching requirements are less stringent [26, 87, 99].

GENETIC CONSIDERATIONS FOR HSCT

Genetics are an important consideration in HSCT due to self versus non-self recognition by the immune system. Genetic disparities between the donor stem cells and the recipient host can lead to an immunologically mediated systemic disorder known as graft-versus-host disease (GVHD). Immunologically, it is advantageous to transplant genetically identical stem cells and this occurs in the settings of syngeneic or autologous HSCT. During a **syngeneic** transplant, stem cells are given from a genetically identical host. Although this situation is possible for identical twins and is commonly used with inbred laboratory animals, it is not likely within the general public. What is more common is an **autologous** transplant, where stem cells are collected from the patients themselves prior to myelo- and/or lympho-ablative conditioning. These autologous stem cells are then reinfused as rescue therapy following irradiation. Autologous and syngeneic HSCTs have the advantage of being fully compatible for both major and minor histocompatability antigens. Finally, an **allogeneic** transplant is when the stem cells are from a genetically unrelated donor where histocompatability antigen mismatches are present (Table 2). The most adverse post--transplant reactions occur in allogeneic transplants when donor lymphocytes recognize host tissues (such as the skin, gut, and lung) as foreign, which results in GVHD (reviewed in [26]). However, there are situations where minor mismatches also can be beneficial. Minor mismatches are able to invoke a graft-versus--leukemia response which may assist the donor lymphocytes in their ability to eradicate residual host leukemic cells [11]. Currently, autologous transplants outnumber allogeneic transplants by about 2:1 [26].

CONDITIONING REGIMENS

There are a variety of different conditioning regimens utilized to prime the host for acceptance of HSCT. Initially, a myeloablative dose of total body irradiation

Table 2. Types of HSCT

Autologous	Patients receive their own stem cells	No mismatch
Syngeneic	Patients receive stem cells from a genetically identical donor	No mismatch
Allogeneic	Patients receive stem cells from their brother, sister, or parent. Stem cells may also come from an unrelated donor	Minor/major mismatch

(TBI) was used to ablate cancers and to eradicate the host of their natural stem cells, thereby creating a niche to allow engraftment of the donor stem cells [26, 51]. Toxicity associated with TBI lead to protocols using multiple lower doses of irradiation with shielding of organs to reduce injury associated with the conditioning regimen. In the last two decades it has become common to use chemotherapy drugs such as cyclophosphamide and busulfan, alone or in conjunction with TBI, to ablate the recipient BM [26]. Today, some transplants are performed using reduced-intensity non-myeloablative treatments which decrease the toxicity and neutropenia associated with the more aggressive treatments. However, this is not always advantageous since, in the case of HSCT for cancer, there is a higher chance of relapse [56].

NONINFECTIOUS HSCT COMPLICATIONS

A myriad of complications can occur as a result of HSCT therapy. The majority of deaths associated with HSCT result from GVHD; however, there are other complications that occur as a result of the conditioning regimens. Some of these complications are multi-system problems, such as continued cytopenias resulting in bleeding [81], renal dysfunction [48], veno-occlusive disease [15], and systemic chronic GVHD [26, 73]. Pulmonary complications (both infectious and noninfectious) are particularly prevalent and are reported in up to 60% of HSCT patients, accounting for high morbidity and mortality [86]. The complications in the lung following HSCT include both infectious and noninfectious pneumonitis, GVHD, bronchiolitis obliterans (BO), and pulmonary vascular abnormalities [52].

Noninfectious pulmonary complications post-HSCT can be either acute (such as idiopathic pneumonia syndrome – IPS) or chronic (such as BO) [103] and are often related to GVHD. The median onset for IPS occurs 21–65 days after transplant, when symptoms such as shortness of breath, dry cough, and hypoxemia with or without fever appear [1, 103]. IPS mortality is reported to be as high as 80% and is associated with alveolar injury [103]. A chemokine-driven recruitment of inflammatory and immune-effector cells to the lung and the release of oxidants and proinflammatory cytokines is

thought to initiate IPS [25]. Allogeneic transplant patients are at even greater risk due to a second wave of injury mediated by alloreactive T lymphocytes [1, 103].

Patients can also develop late pulmonary complications at greater than 100 days post-transplant [103]. The incidence of late-onset pulmonary complications ranges from 20–50% depending on donor source and the time post-HSCT [103]. These can present as restrictive lung diseases, such as BO with organizing pneumonia, and interstitial pneumonias and fibrosis secondary to drug toxicity [103]. More commonly, patients develop BO associated with chronic GVHD 80–700 days post-HSCT [51, 1]. This is characterized by inflammation and fibrosis of the small airways leading to a fixed obstructive ventilatory defect occurring almost exclusively in allogeneic transplants and in patients with other evidence of chronic GVHD. There is substantial mortality associated with BO and treatment options are limited [1, 103].

INFECTIOUS HSCT COMPLICATIONS

Infectious complications are a common cause of morbidity and mortality following HSCT. Serious infections occur within the first two years in 50% of patients receiving HSCT from matched sibling donors [32]. However, the rate of infection can be as high as 90% in patients receiving HSCT from matched unrelated donors or in patients who develop GVHD [32]. Additionally, the use of immunosuppressive therapies in allogeneic transplant recipients to treat GVHD can further increase the risk of developing a serious infectious complication [32]. Despite numerous advances in prophylactic strategies, diagnosis, and treatment, pneumonia remains the leading infectious cause of death after HSCT [51].

Post-HSCT there are three phases of susceptibility: the first month after transplant prior to hematopoietic engraftment (neutropenic stage), the second through third month after transplant (engraftment or immune reconstitution), and three months or later after transplant (post-engraftment) [102]. During the first month post-HSCT, immune reconstitution is not complete and patients are extremely susceptible to bacterial, viral, and fungal infections [24, 51]. One study indicated that over 80% of patients had either clinical or microbiologically significant bacterial, fungal, or viral infections during the neutropenic stage post-HSCT [40]. Aspergillosis is an especially dangerous threat to both allogeneic and autologous HSCT recipients during the pre-engraftment period [51]. Bacterial pneumonia caused by Gram-negative pathogens, especially *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*, occur most often during the first 100 days post-transplant [51]. Among aerobic Gram-negative pathogens, *P. aeruginosa* has the highest associated mortality rate (40%) [24]. Cytomegalovirus is the most frequent and most virulent organism associated with pneumonitis during the second phase, with approximately 50% mortality [28]. In contrast, bacterial pneumonitis, bacterial septicemia, and sinusitis associated with Gram-positive organisms have been reported as the most frequent infections occurring six months after HSCT [52]. Although immune reconstitution is said to occur by day 100, clinical studies document that HSCT patients exhibit long-term immune dysfunction for months or even years post-transplantation [6].

INNATE IMMUNITY IN THE LUNG

The lung has the largest interface with the external environment of any internal organ and requires an elaborate host defense system to protect it [104]. The immune system has several different components, which include the adaptive component (T and B cells), the innate component (macrophages/monocytes, polymorphonuclear leukocytes (PMNs), and natural killer (NK) cells), and dendritic cells (DC), which serve as mediators between the adaptive and innate immune systems. The adaptive immune system has the capacity to recognize almost any antigenic structure regardless of whether the motif is bacterial, environmental or self in origin [105]. T and B cell receptors are not encoded in the germline and are uniquely generated during cellular development [68, 105]. Therefore, a diverse repertoire of receptors is generated randomly, and those receptors that escape positive and negative selection are subsequently selected for clonal expansion when they encounter their specific antigen [68, 105]. The clonal expansion of lymphocytes is often necessary for the generation of an effective immune response and the clearance of a pathogen; however, it takes at least five days for sufficient numbers of clones to be produced and to differentiate into effector cells [68]. Thus the innate immune system, which includes antimicrobial peptides, phagocytes, and the alternative complement pathway, serves as the initial defense against microorganisms and also plays a pivotal role in the activation of the adaptive immune system [68, 104].

Innate immunity includes both nonspecific structural and mechanical defenses as well as specific cell-mediated mechanisms. Cilia, cough reflex, and mucus clearance are a variety of nonspecific features which protect the lung from potential extracellular invading pathogens [104]. Resident lung macrophages and recruited PMNs are key cells for the generation of cell-mediated innate immune responses [9, 29]. Although phagocytes play a major role in host defense, they can also cause considerable damage if left unregulated. For example, inadequate or unrestrained activation of either macrophages and/or PMNs result in uncontrolled release of oxidants and proteolytic enzymes which could lead to tissue and vasculature destruction [90].

Macrophages

In a non-diseased state, macrophages represent the majority of bronchoalveolar cells (>85%) in the lower

respiratory tract [32, 64, 90]. It is believed that macrophages found in the lung originate from either blood monocytes or proliferation by resident alveolar macrophages (AMs) [90]. There are several different subtypes of lung macrophages identified as morphologically and functionally heterogeneous from one another, including alveolar, interstitial, intravascular, and airway macrophages [90]. Of note, AMs are believed to be long-lived radio- and chemotherapy-resistant cells and they are slow to turn over and be replaced by donor-derived cells following HSCT [57, 58, 65, 71, 74, 93, 94]. Cell-surface receptors and secreted products allow lung macrophages to respond to environmental factors and aid in the clearance of microorganisms in the distal airways and alveolar spaces [90, 104]. In the lung, macrophages function as professional antigen-presenting cells (APCs) by processing and presenting pathogen peptides on their MHC II receptors [29]. Although it is known that AMs specifically are relatively poor APCs, they do function to carry microbial antigens into the interstitium and to the regional lymph nodes, where they are taken up by DCs and presented to lymphocytes to initiate adaptive immune responses [64]. Macrophages also contain receptors for both antibody and complement, which serve as opsonins to enhance the phagocytic capacity of these cells [29]. Macrophages are also capable of destroying or breaking down the microorganisms they have engulfed through the release of oxygen radicals, namely superoxide anion, hydrogen peroxide, hydroxyl radical, and proteolytic enzymes such as lysozyme, elastases, and collagenases [29, 90]. Interestingly, macrophages are also able to secrete antioxidants, antiproteases, and inhibitors of cytokines to control and dampen the immunological insult after containment and clearance has occurred [77].

PMNs

Lung macrophages also contribute to the inflammatory process through their ability to recruit additional cells, such as PMNs, to the site of inflammation [44, 90]. PMNs normally account for approximately 1% of bronchoalveolar cells and are absent from the distal airways and alveoli. However, PMNs are able to migrate from the pulmonary vasculature when activated by appropriate stimuli. AMs are capable of secreting PMN chemoattractants, such as leukotriene B_4 (LTB_4) and IL-8, that cause PMNs to undergo morphologic and functional changes enabling them to migrate into the airways [29, 90]. PMNs follow chemoattractant gradients to the site of infection via the upregulation of specific cell-surface adhesion receptors allowing migration through the vessel walls and into the airways [29]. During a robust microbial insult it is likely that the total number of PMNs will outnumber the total number of macrophages present [9, 12, 74, 90]. Like other phagocytes, PMNs produce a variety of secretory molecules to aid in the phagocytosis and killing of pathogens in the lung. PMNs, through a membrane-associated NADPH-dependent oxidase, release many of the same reactive oxygen metabolites as macrophages [50, 90]. PMNs also store enzymes, such as elastase, hydrolase, myeloperoxidase, lysosyme, and neutral serine proteases, in their azurophilic granules which can serve as potent bactericidal agents [90].

NK cells

Another important cell in the innate immune system are the NK cells which are derived from the BM and circulate in the blood [59]. These cells are able to recognize both endogenous and exogenous glycolipid antigens presented by CD1d, which is a non-polymorphic surface protein related to the classical MHC I molecule [98]. NK cells are activated early in an immune response by cytokines or by encountering a target cell that expresses the ligands for the NK cell receptor. Like conventional lymphocytes, some NK cells express a T cell receptor. However, unlike T and B cells, the receptor is encoded by the germline and does not undergo somatic recombination and is thus considered semi-invariant [59, 98]. NK cells are also different from conventional lymphocytes because these cells lack immunological memory [59, 98]. NK cells are capable of using two different mechanisms to control infection: the secretion of the immune-activating cytokines IFN-γ and/or TNF-α and the direct lysis of infected cells by exocytosis of granules that contain perforin and granzymes [29, 59]. It is the balance of signals from both activating and inhibitory receptors that determines the outcome of NK cell activity. Inhibitory receptors on the NK cell recognize MHC I molecules, which are present on virtually all cell types. The loss of MHC I molecules, possibly because of an infection, can lead to NK cell activation, which allows these cells to recognize "missing self" [59]. Activating NK receptors are able to bind to host-derived or pathogen-encoded ligands that are upregulated on infected cells, resulting in either lysis of the cell or the production of pro-inflammatory cytokines [59].

Dendritic cells

DCs are considered to be the professional APCs of the body. Immature DCs circulate throughout the body surveying for evidence of infection using non-specific receptors (discussed below). Once a pathogen is encountered, DCs engulf the organisms, secrete activating cytokines, mature, and move quickly to the draining lymph node. Once in the secondary lymphoid system, the mature DCs serve to activate specific T cell responses (helper cytokine secretion and/or cytotoxic T cell generation) and B cell responses (antibody production) [41].

Toll-like receptors

Unlike the adaptive arm of the immune system, the innate immune system does not recognize each pathogen individually; rather it focuses on a few highly

conserved structures that are present in large pathogenic groups [68]. These structures are referred to as pathogen-associated molecular patterns (PAMPs) and the receptors that have evolved to recognized them are pattern-recognition receptors, or more commonly called Toll-like receptors (TLRs) [68]. Some of the most well--known examples of PAMPs are Gram-negative bacterial lipopolysaccharide, peptidoglycan, Gram-positive lipoteichoic acids, flagellin, bacterial DNA, double--stranded RNA, and glucans [68]. Although the ligands are chemically unrelated, PAMPs do have several common features, including relatively unique production by microorganisms, structures essential to the survival or pathogenicity of the microbe, and components shared by entire classes of pathogens [68].

TLRs have a major role in the induction of immune and inflammatory responses by their ability to differentiate between "host" and "foreign" antigens. The TLRs are a highly conserved family of type 1 transmembrane receptors characterized by an N-terminal extracellular leucine-rich domain and a C-terminal intracellular domain that is homologous to the IL-1 receptor [104]. To date, 10 human and 13 murine TLRs have been identified to bind to an array of bacterial, fungal, and viral products [64]. All of the known TLRs signal via their intracellular tails by activating a cascade of intracellular kinases leading to diverse gene expression. One of the main transcriptional factors activated by the TLR pathway is NF-κB, which translocates to the nucleus when activated to transcribe important inflammatory gene products [64]. Interestingly, TLR expression is not limited to leukocytes and was also been found on the surface of structural cells, such as lung epithelial cells [42, 64, 75] and mesenchymal cells [54]. TLRs have recently been shown to modulate airway responses to ozone and asthma as well as infection [64].

INNATE IMMUNE RECONSTITUTION

Reconstitution is the repopulation of the immune and hematopoietic systems of the recipient and is dependent on appropriate proliferation, maturation, and differentiation of donor cells [61]. Successful homing and engraftment of donor stem cells into the host is a variable process in which reconstitution of effector cell function does not necessarily correlate with recovery of cell numbers [6]. Most HSCT recipients have some type of immune dysfunction regardless of the type of graft (autologous, syngeneic, or allogeneic), the type of underlying disease, the conditioning or preparative regimen, the type of post-transplant immunosuppression, or the presence of GVHD [6, 61, 101]. Thus a better understanding of the factors that regulate these dysfunctions is sorely needed.

The kinetics of immune reconstitution follows a generalized scheme. Peripheral phagocytes and NK cells are the first cells to be reconstituted post-HSCT in human transplant recipients [5, 61]. After the initial reestablishment of phagocytes, there is repopulation of early lymphoid cells responsible first for primitive and then for more specific functions, such as proliferation, helper activity, differentiation, cytokine production, and antibody synthesis [61]. It is believed that these latter functions require complex and finely tuned cell-cell interactions mediated by cell contact and soluble factors, which may be why they appear later in the reestablishment of the immune system [61].

PMN reconstitution

The first phagocytic cells to recover after HSCT are the PMNs, which are normally present 2–4 weeks post--transplant [6]. The total number of PMNs appears to normalize early post-transplant [61]; however, cellularity does not necessarily correlate with complete functional recovery [6]. There are some conflicting studies as to the functional ability of PMNs post-HSCT. Researchers found that reconstituted PMNs had diminished or impaired chemotaxis, superoxide production, and bactericidal activity for at least two months after allogeneic HSCT [5]. Similarly, impairment in chemotaxis, superoxide induction, and phagocytic function was found months to years post-transplant in PMNs from patients receiving autologous transplants [106]. In contrast, one study showed there to be no difference in the phagocytic or oxygen-dependent intracellular killing mechanism of PMNs isolated early in the reconstitution period compared with cells from normal controls [61]. Our animal models have suggested that PMNs post-syngeneic HSCT may recover phagocytic function, but remain impaired in bactericidal killing [8, 74].

Macrophage reconstitution

As opposed to PMNs, macrophages are not reconstituted for weeks to months post-transplant [6, 65, 74]. Peripheral blood monocytes are donor-derived by day 41 post-transplant, whereas tissue-fixed macrophages in the lung and liver are of donor origin beginning at 80 days post-HSCT [61]. Resident AMs are capable of surviving ablative cytotoxic therapy and can persist in the lungs for up to 90 days after allogeneic transplant [100]. Animal studies suggest that the delay in AM reconstitution could be even longer post-HSCT [6, 65, 74]. Delayed AM maturation could help explain the increased prevalence of lung infections post-HSCT. Once again, controversy exists as to the functional ability of these cells after reconstitution. Defects such as impaired chemotaxis, phagocytosis, and killing have been documented in AMs from allogeneic HSCT patients [102]. However, studies have also shown that peripheral monocytes exhibit normal chemotaxis, adherence, phagocytosis, and cytotoxicity early post-engraftment and are able to function as professional APCs by presenting killed *E. coli* bacteria in proliferation assays [61]. These data could also highlight anatomic differences in the functional recovery of macrophages. In support of this hypothesis, our work in

a murine model of syngeneic HSCT suggests that AM function is persistently impaired post-transplant (see below).

NK cell reconstitution

After an autologous HSCT, NK cell numbers are normalized quickly within 30–50 days after transplantation [5]; however, up to 20% of marrow recipients have defective cytotoxic functions a year or more post-transplant [61]. In most patients there is an early recovery of antibody-dependent cytotoxicity and tumor cell lysis post-HSCT. Thus, unlike phagocytes, it appears that the kinetic recovery of NK cells coincides with functional recovery in most HSCT patients [6].

Dendritic cells

As mentioned earlier, DCs serve to link innate and adaptive immunity. Donor-derived DCs were found as early as 14 days after allogeneic HSCT [5]; however, the kinetics of immune reconstruction are dependent on the source of the stem cell and the conditioning regimen [6]. There are reduced total numbers of circulating plasmacytoid and myeloid DCs early after allogeneic HSCT; however, they reach normal levels approximately one year post-transplant [85]. Following autologous transplant, DCs generated from precursor populations within the peripheral blood of transplant patients have significant antigen-presenting capacity [6]. Studies also suggest that early DC recovery may serve to protect the transplant recipient against infection in lieu of a functional adaptive immune response early post-HSCT [6]. Murine allogeneic HSCTs have shown that residual host DCs initiate acute GVHD by priming donor T cells reactive against the host [85]. Even immature myeloid DCs have been shown to activate the proliferation of naïve allogeneic T cells [85].

EICOSANOID SYNTHESIS

Eicosanoids are lipid mediators that function in much the same way as classically known peptide mediators such as cytokines, chemokines, or hormones. The Nobel Prize was awarded to three investigators for their work on the structure, biosynthetic pathway, pharmacologic modulation, and biological actions of eicosanoids [39]. Eicosanoids are known to modulate a variety of different biological responses, ranging from muscle contraction to intracellular regulation of gene transcription. These unique lipid mediators are capable of being synthesized and secreted within minutes of stimulation by virtually all cell types [39, 78]. Eicosanoids elicit a wide range of biological responses by binding to their corresponding G-protein-coupled receptors (reviewed in [39]). The main precursor for these lipid mediators is arachidonic acid (AA), which is cleaved from the cell membrane-associated phospholipids via the phospholipase A_2 enzymes. For the purpose of this review we will only be examining two byproducts of the eicosanoid pathway, prostaglandins (PGs) and leukotrienes (LTs) (see Fig. 1). PGs are generated through the action of cyclooxygenase (COX) enzymes, which convert AA to an unstable intermediate molecule, PGH_2. Through the actions of additional synthase enzymes, PGH_2 is rapidly converted to other terminal PG products, such as prostacyclin (PGI_2), $PGF_{2\alpha}$, PGD_2, PGE_2, and thromboxane A_2 [39]. There are actually two isoforms of the COX enzyme: COX-1, which is known for constitutive or homeostatic activity, and COX-2, which is the inducible form responsible for many of the inflammatory effects of PGs [76]. Of particular interest, the COX enzymes are the targets for nonsteroidal anti-inflammatory drugs, such as indomethacin and aspirin, and for other selective COX-2 inhibitors, such as Vioxx® and Celebrex® [31, 76]. Conversely, AA can also be converted into LTs through the action of the calcium-dependent enzyme 5--lipoxygenase (5-LO) and its helper protein 5-LO activating protein (FLAP) [78]. Similar to the PG pathway, the first LT generated is an unstable epoxide, LTA_4, which is rapidly hydrolyzed via LTA_4 hydrolase to form LTB_4 or is conjugated with a glutathione molecule by LTC_4 synthetase to form LTC_4. The removal of amino acids from glutathione through additional enzymes can convert LTC_4 into LTD_4, which is subsequently converted into LTE_4 [39]. LTC_4, LTD_4, and LTE_4 are collectively known as the cysteinyl LTs (cys-LTs).

LT signaling and actions in mediating innate immunity

When secreted by activated cells, LTs cause a wide spectrum of biological responses. LTB_4 is most com-

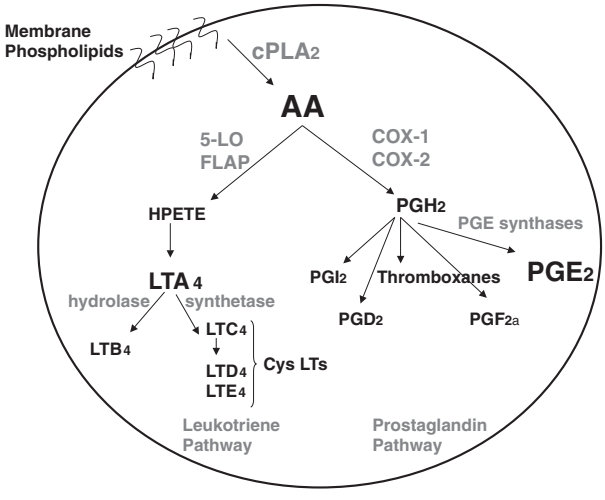

Fig. 1. Eicosanoid synthesis in innate immune cells: AA is released from membrane phospholipids and can be metabolized to form either leukotrienes or prostaglandins. Leukotrienes have positive effects on immune functions, whereas prostaglandins are inhibitory for these same functions.

monly known for its role as a potent PMN chemoattractant [22]. On the other hand, the cys-LTs have gained attention as important mediators in asthma [27]. However, LTs are less known and appreciated for their role in innate immunity [78]. Both macrophages and PMNs are able to synthesize and secrete LTs and have LT receptors on their cell surface [22, 39, 78]. The role of LTs in host defense gained attention when it was demonstrated that 5-LO deficient mice had decreased survival and impaired bacterial clearance in the lung when infected with *K. pneumoniae* [7]. Subsequent studies have shown a role for LTs in augmenting bacterial phagocytosis and killing by AMs [7, 63, 89] and PMNs [21, 22, 62], inducing TNF-α production by AMs [69] and PMNs [88], and recruiting PMNs to the site of infection [96].

LTs mediate their effects via binding to specific cell-surface G-protein-coupled receptors. LTB_4 can interact with one of two receptor isoforms, BLT1 or BLT2 [78]. Most of the recognized actions of LTB_4 can proceed through the BLT1 receptor. Interestingly, cys-LTs can also interact with two different receptor isoforms, cys-LT1 and cys-LT2. Most biological activity is regulated through cys-LT1, and LTD_4 is known to have the highest affinity for this receptor [35, 70]. When LTB_4 or cys-LTs bind to their respective receptors, they activate Gq and Gi proteins to increase the intracellular Ca^{2+} levels and decrease cyclic AMP (cAMP), respectively [78]. These LTs are able to activate a number of downstream pathways involving protein kinase C, MAP kinases, phosphatidyl inositol-3-kinase, Rac, NF-κB, and reactive oxygen intermediates. In terms of host defense, the net result of LT signaling is generally to enhance phagocyte engulfment and killing.

PG signaling and actions in mediating innate immunity

PGs are known to play a role in a variety of homeostatic and pathologic processes. PGE_2 has been shown to have proinflammatory action by mediating endothelial cell vasodilatation, which facilitates the recruitment of circulating leukocytes to an infected area [30]. In addition, PGE_2 is capable of enhancing leukocyte production of the proinflammatory cytokine IL-6 [66]. As opposed to LTs, however, PGs exert profound negative effects on host defense functions. Although phagocytes are capable of producing a variety of PG byproducts, we will focus on the regulatory functions of PGE_2. PGE_2 is able to inhibit the following: leukocyte chemotaxis [2], AM phagocytosis and killing [3, 4], PMN host defense functions [45], reactive oxygen intermediate production [67], AA release [34], LT synthesis [17], and the generation of multiple proinflammatory cytokines [13, 46, 53]. PGE_2 also enhances the production of the immunosuppressive cytokine IL-10 [43].

PGE_2 is capable of exerting a wide variety of responses in different cells due to its ability to bind to four different receptor isoforms, which are termed E prostanoid (EP) receptors 1 through 4 [72]. Each of these four receptors couples to distinct G proteins with diverse intracellular signaling pathways. Lung AMs and PMNs express all four EP receptors, with their expression order as follows: EP2>EP3>EP1>EP4 (our unpublished observation). The EP2 and EP4 receptors are Gs coupled and signal by increasing intracellular cAMP levels [72]. Previous work has shown that PGE_2 inhibits AM phagocytosis via signaling through the EP2 receptor and raising intracellular cAMP levels [3]. PGE_2 inhibition of AM phagocytosis involves the activation of the guanine exchange protein activated by adenyl cyclase (EPAC-1), whereas bactericidal killing in AMs is mediated through activation of both EPAC and protein kinase A [3, 4].

EICOSANOID DYSREGULATIONS IN DISEASE

It has been previously shown that eicosanoid dysregulation is implicated in a variety of immunosuppressed and disease states. For example, impaired LT synthesis has been noted in HIV infection [21], cigarette smoking [10], post-sepsis [20], diabetes mellitus [47], vitamin D deficiency [23], cirrhosis [19], malnutrition [91], and neonates [60]. Moreover, increased PGE_2 production has been noted in cancer [16], aging [38], HIV infection [82], malnutrition [84], and stem cell and solid organ transplant recipients [14, 33]. Importantly, PG blockade has also been shown to improve host defense in models of sepsis [83, 95] and pneumonia [37, 92]. Thus a myriad of previous studies have all shown that eicosanoids can play a role in the progression and regulation of a variety of diseases states.

We have been interested in whether eicosanoids play an important role in the immunosuppression seen in patients following HSCT. Normally, AMs in the lung produce LTs, and these are stimulatory for cellular influx, phagocytosis, and killing of microorganisms [18, 78–80]. However, TBI used as a conditioning regimen causes resident lung cells to upregulate PGE_2 production as a consequence of exposure to ionizing radiation [97]. PGE_2 can in turn diminish the production of LTs by AMs and limit the host-defense functions of these cells [3, 17]. Previous work has shown that HSCT patients, regardless of conditioning regimen or stem cell source, have elevated levels of PGE_2 in their plasma [14]. Additionally, PGE_2 can suppress lymphocyte function in human HSCT recipients, which was reversible *in vitro* by pharmacological COX inhibition [49]. It was also shown that the direct application of PGE_2 to the oral mucosa of patients after transplantation increased the risk of reactivating latent herpes simplex virus infections [55]. Our studies in a murine syngeneic HSCT model suggest that LT production by lung phagocytes is reduced post-transplant while PG production is elevated (see below), implying an eicosanoid dysregulation post-HSCT.

DYSREGULATION OF EICOSANOIDS POST-HSCT; STUDIES FROM AN ANIMAL MODEL

Our lab previously generated a murine model of HSCT where BM from a syngeneic mouse repopulates a recipient mouse whose BM has been obliterated by TBI. Using this model we have shown that 21 days post--transplant the majority of the lung leukocytes and splenocytes are donor derived [74]. Similarly, when control (untransplanted) and HSCT mice are challenged with a Gram-negative *P. aeruginosa* infection three weeks post-HSCT, there was no difference in the cellular recruitment between transplanted and untransplanted control mice [74]. However, despite the cellular reconstitution, the HSCT mice are more susceptible to pulmonary infection with *P. aeruginosa*, implying that there were HSCT-related functional defects in the lung phagocytes [74]. Additional work demonstrated that this was due, in part, to an impairment in the ability of AMs, but not PMNs, to phagocytose Gram-negative bacteria both *in vitro* and *in vivo* post-HSCT [74]. Assessment of bacterial killing activity concluded that both AMs and PMNs from the HSCT mice were defective [8].

More recently we examined the eicosanoid synthesis of the innate immune cells post-HSCT. Post-HSCT we found increased PGE_2 in the bronchoalveolar lavage fluid as well as whole lung homogenates from HSCT mice compared with control mice [8]. At baseline, HSCT AMs produce 125-fold more PGE_2 than do control AMs. Similarly, HSCT PMNs produce 10-fold more PGE_2 compared with untransplanted control cells [8]. Interestingly, HSCT AMs, but not PMNs, produce half the amount of LTs when optimally stimulated. This dysregulation in eicosanoids corresponds to increases in the expression of COX-2 and PGE_2-synthase and decreased FLAP expression in phagocytes from BMT mice [8]. Because of the role of PGE_2 in phagocyte function, AMs were treated *in vitro* with indomethacin, a COX inhibitor. The ability of HSCT AMs to phagocytose both opsonized and non-opsonized bacteria was restored *in vitro*. In addition, indomethacin treatment restored the defect in bacterial killing seen in both AMs and PMNs isolated post-HSCT [8].

Pharmacologic and genetic approaches were used to verify the effects of blocking PGs *in vivo* and to determine whether this approach influenced survival of bacterial pneumonia post-HSCT. HSCT mice were given a dose of indomethacin at 1.2 mg/kg at the same time that they were given a bacterial infection with *P. aeruginosa*. Twenty-four hours post-infection there was decreased bacterial burden in the lung and bacterial dissemination in the blood of BMT mice treated with indomethacin compared with vehicle control-treated HSCT mice [8]. In addition, there was no difference in the amount of PGE_2 found in the lung homogenates in the HSCT mice treated with indomethacin compared with control untransplanted mice. To test this hypothesis genetically, BM was harvested from heterozygous (PG-deficient) COX-2 mice and transplanted into control mice. The AMs from the chimeric COX-2 HSCT mice phagocytosed bacteria better *in vitro* than did control HSCT mice, but they did not reach the levels of AMs from untransplanted mice [8]. Additionally, we verified that AMs overproduce PGE_2 following HSCT when the conditioning regimen involves chemotherapy (busulfan treatment) as opposed to TBI (unpublished observation). Thus these results in an animal model strongly suggest that overproduction of PGE_2, and perhaps underproduction of LTs, post-HSCT can have profound negative effects on pulmonary host defense (Table 3). Fortunately,the strategies which limit PG production in the murine HSCT model appear to have valid therapeutic potential.

Table 3. Eicosanoid alterations that occur post-HSCT and the effect on innate immunity

Eicosanoid alteration	Innate immune effect
Decreased LTB_4 and cys-LT production (decreased 5-LO and FLAP)	Diminish PMN recruitment Diminish PMN function Inhibit AM phagocytosis and killing
Increased PGE_2 production (enhanced COX-2 and/or PGE synthases)	Diminish LT production Inhibit PMN bacterial killing Inhibit AM phagocytosis and killing

CONCLUSION

The effective use of HSCT to treat a variety of malignant and inherited diseases is limited by the prevalence of complications involving pulmonary infections post-HSCT. Restoration of innate immunity in the lung post-HSCT involves both cellular and functional reconstitution of donor-derived stem cells. We have reviewed evidence to suggest that functional recovery of the innate immune cells lags behind cellular recovery in both human and animal models of HSCT. Furthermore, evidence from both human and animal studies demonstrates that PGE_2 production is elevated post-HSCT. Given the well-characterized inhibitory actions of PGE_2 on lung phagocyte function, it is perhaps not surprising that this dysregulation can impair host defense. Animal models suggest that strategies which block PG production post-HSCT can dramatically improve survival of Gram-negative infections post-HSCT. Further studies are needed to verify that this dysregulation of eicosanoid synthesis is present in human lung phagocytes post-HSCT and to determine whether strategies which limit PG synthesis or signaling may improve outcomes for HSCT patients.

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