The Chemokine System: A Possible Therapeutic Target in Acute Graft Versus Host Disease

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Contents

Abstract Allogeneic hematopoetic stem cell transplantation often presents the only chance for cure in a number of malignant and nonmalignant hematologic diseases. However, its beneficial effects are counterweighed by the development of potentially lethal complications, most importantly the development of acute and chronic graft-vs.-host disease (GVHD). Alloantigen-reactive immune responses mediate injury and destruction of GVHD target organs, including the gastrointestinal tract, the liver, the skin, and the lung. Donor leukocyte infiltration into the respective tissues is orchestrated by interactions between chemokines and chemokine receptors, which will be reviewed using a basic science – clinical comparative approach.

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1 Introduction

For numerous malignant and nonmalignant diseases, allogeneic hematopoetic stem cell transplantation (HSCT) is the only curative treatment available today. However, its use and benefits are limited by the development of serious and life-threatening complications, most importantly, acute and chronic graft-vs.-host disease (GVHD), both of which are major causes for morbidity and treatment-related mortality (TRM). The pathophysiology of acute GVHD (aGVHD) has been a strong focus of both clinical and basic science over the last decades. The current concept involves three phases as follows: (1) conditioning toxicity to host tissue with subsequent expression of inflammatory cytokines and chemokines, resulting in the activation of host antigen presenting cells (APCs), (2) donor T cell activation, expansion, and differentiation, and (3) host tissue injury by infiltrating donor immune cells through direct cell to cell related mechanisms of cytotoxicity and the production of soluble cytotoxic mediators (Goker et al. 2001; Ferrara et al. 2009).

Distinct from aGVHD, chronic GVHD (cGVHD) pathophysiology is rather less understood, as both autoimmune-like processes, alloreactive T cells (Sullivan and Parkman 1983; Teshima et al. 2003; Cutler et al. 2001; Champlin et al. 2000), a shift from a Th1 to a Th2 immune response (Kataoka et al. 2001), immunodominant epitope-dependent organ involvement (Kaplan et al. 2004), and B-cell (auto-) antibody-production (Okamoto et al. 2000) seem to play a role.

Chemokines and their receptors comprise a complex system involved in leukocyte migration to target tissues and to inflammatory sites, in leukocyte activation, in the organization and structure of secondary lymphoid tissues, in hematopoiesis, and in angiogenesis (Pease and Williams 2006; Moser et al. 2004; Rollins 1997; Choi et al. 2007; Addison et al. 2000; Belperio et al. 2000; Strieter et al. 2005; Broxmeyer 2008; Ohl et al. 2003; Czermak et al. 1999; Muller et al. 2003). Following allogeneic HSCT, they are increasingly expressed in various GVHD target organs and contribute to organ injury and TRM (Mapara et al. 2006; New et al. 2002; Sugerman et al. 2004; Jaksch et al. 2005; Duffner et al. 2003; Hancock et al. 2000; Hildebrandt et al. 2004a, b, c, 2005; Piper et al. 2007; Terwey et al. 2005; Varona et al. 2005; Wysocki et al. 2004, 2005a, b; Bouazzaoui et al. 2009).

This article reviews the role of specific chemokines and their receptors in aGVHD and cGVHD and elucidates their potential as a target for preventive therapy or actual treatment of these deleterious complications following allogeneic HSCT.

2 Allogeneic Hematopoetic Stem Cell Transplantation and Graft Versus Host Disease

For many children and adults with hematologic malignancies (e.g., leukemia, lymphoma, and multiple myeloma) or nonmalignant diseases, including hemoglobinopathies and metabolic storage diseases, allogeneic HSCT provides the only

therapeutic option, with a potential for long-term remission and even cure. Until a few years ago, conceptual understanding of allogeneic HSCT in the treatment of cancer was based on the idea that lethal total body irradiation and high dose chemotherapy are critical means to fight underlying malignancy to the optimal extent, but at the same time will result in irreparable damage to the patient's hematopoesis. The purpose of transfusing donor stem cells that time was to rescue the patient from the emerging state of hematopoetic failure and fatal immunoin-sufficiency. Nowadays, in the treatment of hematologic malignancies, the idea has shifted towards allogeneic HSCT as being the platform for long-lasting graft-vs.-leukemia (GVL) or graft-vs.-tumor (GVT) responses and adoptive immunotherapy, both of which imply alloantigen-specific and immunologically mediated disease eradication and surveillance (Truitt and Atasoylu 1991a, b; Oettel et al. 1994; Slavin et al. 1993; Fowler et al. 1996, 1997; Nash and Storb 1996; Barrett 1997; Datta et al. 1994; Fowler and Gress 2000; Riddell et al. 2002; Kolb et al. 2003; Mapara et al. 2003).

The clinical use of HSCT is nevertheless limited by the potential development of severe and life-threatening complications. Besides the increased risk for infections due to extensive immunosuppression, the most common and well described risk is GVHD.

Differences in the human leukocyte antigen (HLA) system between the stem cell donor and the recipient result in severe T cell-mediated inflammatory reactions against host tissue(s), which are summarized under the term "GVHD." However, GVHD can also be seen in completely HLA-matched transplantation due to immunologically relevant minor histocompatibility antigens (HAs) (Ferrara et al. 2009; Goulmy et al. 1996). According to former concepts to classify GVHD, acute disease (aGVHD) was distinguished from chronic disease (cGVHD) according to the time point of onset (before or after day 100 after transplantation). Nowadays, this concept has been modified, as with the introduction of reduced-intensity conditioning (RIC) regimens, late onset forms of aGVHD (appearing >100 days after HSCT) as well as an overlap syndrome sharing features of both acute and chronic disease are more frequently seen (Ferrara et al. 2009; Filipovich et al. 2005).

Incidence and severity of GVHD are related to the degree of HLA mismatch between donor and recipient, the amount of transplanted donor T cells within the graft, patient's age, and the chosen conditioning regimen (myeloablative vs. RIC), with an incidence ranging from 10 to 80%. Target organs in aGVHD include the immune system, skin, liver, gastrointestinal (GI) tract, and lung, and mortality can be as high as 95% (Ferrara et al. 2009; Cooke et al. 1998; Miklos et al. 2008; Cahn et al. 2005).

The pathophysiology of aGVHD involves three consecutive phases. Phase 1: Tissue damage, caused by the toxicity of the preparative conditioning regimen, is associated with the release of pro-inflammatory cytokines (e.g., TNF, IFNγ) and chemokines and with the activation of host and (later on) donor APCs (Sun et al. 2007; Hill et al. 1997). Phase 2: Antigen-loaded APCs migrate to secondary lymphoid organs, where they encounter and present their antigens to donor

T cells. This results in priming, proliferation, and differentiation of alloreactive CD4+ and CD8+ effector T cells. (Sun et al. 2007; Shlomchik et al. 1999; Teshima et al. 2002). Phase 3: The third phase of aGVHD, also called effector phase, is characterized by alloreactive, cytotoxic T lymphocytes (CTLs) directly infiltrating different GVHD target organs promoting tissue damage via apoptosis. T cell-derived inflammatory cytokines such as TNF, IFNγ, and IL-17 further contribute to target organ injury both on direct cytotoxic levels and indirectly by maintaining a pro-inflammatory environment, responsible for subsequent effector cell recruitment (Sun et al. 2007).

Much less is known about the pathophysiology of cGVHD, which can emerge from acute disease or appear de novo, usually within the first 2 years after HSCT. Its incidence varies from 25 to 80% (Baird and Pavletic 2006), and a limited form is separated from extensive disease, depending on the extent and severity of organ involvement. Recently, the NIH consensus approach for diagnosis and staging of cGVHD provided a scoring system based on the specificity of clinical signs and histopathology (Filipovich et al. 2005). In contrast to aGVHD, every host organ system can be potentially affected, with skin, eyes, oral cavity, GI tract, liver, and lungs being most commonly involved (Baird and Pavletic 2006; Lee 2005). Characteristics of cGVHD include (sub)acute inflammation alongside chronic, fibrotic organ changes. Based on experimental data and clinical observations, a shift towards Th2 immune responses, altered expression of transforming growth factor (TGF)-β, the production of autoantibodies, thymic dysfunction with defective negative selection, and a low regulatory T cell population have been implicated in the development of cGVHD (Teshima et al. 2003; Lee 2005; Martin 2008; Chu and Gress 2008). The response to immunosuppressive treatment is unpredictable and nonuniform, often displaying mixed responses in different organs. Although associated with lower relapse rates due to improved GVT and GVL effects, cGVHD therefore remains the major cause of nonrelapse mortality during long-term follow up after allogeneic HSCT, with 5-year survival rates as low as 40% (Ferrara et al. 2009; Filipovich et al. 2005; Baird and Pavletic 2006; Shulman et al. 1978; Pavletic et al. 2006a; Higman and Vogelsang 2004).

During all phases of aGVHD, chemokines promote and orchestrate the recruitment of immune cells, for example, APCs and effector cells, to secondary lymphoid organs and peripheral tissues. Recent findings that various chemokines like CCL2-5, CXCL1, CXCL9-11, CCL17, and CCL27 are up-regulated during aGVHD underline their pivotal role during this process (Mapara et al. 2006; New et al. 2002; Sugerman et al. 2004; Jaksch et al. 2005; Duffner et al. 2003; Hancock et al. 2000; Hildebrandt et al. 2004a, b, c, 2005; Piper et al. 2007; Terwey et al. 2005; Varona et al. 2005; Wysocki et al. 2004, 2005a, b; Bouazzaoui et al. 2009). In addition, a limited number of reports have recently commented on the chemokine–chemokine-receptor system in cGVHD (Kim et al. 2007; Morita et al. 2007). Therefore, interactions between chemokines and their receptors are of specific interest as potential targets for GVHD therapy and have become a growing focus of intensive research.

3 The Chemokine–Chemokine-Receptor System

Chemokines consist of a group of 8–14 kDa proteins, which signal through a family of seven transmembrane domain-containing G protein-coupled receptors (GPCRs), activating downstream effector pathways (Zlotnik and Yoshie 2000; Rot and Von Andrian 2004). The chemokine–chemokine-receptor system is characterized by a huge degree of redundancy and pleiotropy. Up to date, approximately 50 chemokines and 20 chemokine receptors are known. Chemokines activate different receptors, and at the same time, receptors can interact with multiple ligands. In addition, chemokines as well as their receptors can form functional dimers and high order oligomers, either with partners from their own (homodimerization, -oligomerization) or from a different subfamily (heterodimerization, -oligomerization), thus adding a high degree of variability to an already complex system. Chemokine ligands are currently classified into four families, the CC (CCL1-28), the CXC (CXCL1-16), the CXC3 (CXC3L1), and the XC (XCL1-2) family, depending on the pattern of the first two of four cysteine residues (Allen et al. 2007; Murphy et al. 2000; Murphy 2002; Viola and Luster 2008). The chemokine–chemokine-receptor system plays an important role in organizing and orchestrating leukocyte trafficking both in homeostasis and in states of inflammation. Chemokine expression can be enhanced by inflammatory cytokines (Mackay 2001) and have been associated with different human diseases like infection, autoimmunity, or cancer, in which they serve as chemoattractants, leading immune cells to the sites of antigen priming in secondary lymphoid organs as well as to peripheral tissues in different target organs (Viola and Luster 2008). Secretion and binding of the chemokine ligand to glycosaminoglycans (GAGs), expressed on the surface of endothelial cells, creates a substrate gradient attracting and steering leukocytes equipped with the appropriate receptor to the site of the highest concentration (Allen et al. 2007; Campbell et al. 1998). Leukocytes have been demonstrated to roll along the endothelium of vessels, a process that is regulated by the expression of integrins and selectins on leukocytes and endothelial cells. Concentration and clustering of integrins, caused by signaling events initiated by chemokine–chemokine-receptor binding, leads to high affinity contact of the leukocyte with the endothelium or components of the extracellular matrix at the site of inflammation, and consecutively to an arrest and transmigration through the vascular wall (Campbell et al. 1998; Constantin et al. 2000). But also during homeostasis, leukocytes regularly traffic to secondary lymphoid organs and peripheral tissues to keep up a constant immune surveillance.

4 The Role of the Chemokine–Chemokine-Receptor System in aGVHD

The role of chemokines and chemokine receptors in aGVHD has to been seen in the context of the different organs and the time course of the leading events; early changes have to be differentiated from late(r) events. Also, the expression on

different T cell subsets might play a role. For example, while the administration of CCR2-deficient CD8+ T cells resulted in a significantly decreased extent of leukocyte infiltration in GVHD target organs, unselected CD4+ and CD8+ CCR2−/− T cells had no effect on the course of disease (Terwey et al. 2005). While some chemokine expression studies, in which either the analysis comparing lethal vs. nonmyeloablative conditioning was restricted to the first 10 days after allogeneic HSCT, or in which chemokine expression levels were related to inflammatory organ infiltrates of unconditioned SCID recipient mice (Mapara et al. 2006; New et al. 2002), were limited to a smaller number of chemokines, other studies, looking at higher number of chemokines, were limited to one GVHD target organ only (Sugerman et al. 2004; Ichiba et al. 2003; Zhou et al. 2007). A comprehensive analysis of chemokine and chemokine receptor expression in the four major target organs (GI tract, liver, skin, and lung) of aGVHD following murine HSCT, which has been based on both kinetics and tropism of expression over a time period of 6 weeks, has been recently published by Bouazzaoui et al. (2009). This study provides important information for the initiation and planning of further experimental studies in the search of chemokines and their receptors as potential future targets in the treatment of GVHD. However, certain limitations have to be kept in mind in this study when interpreting this or any other experimental study published in this field up to date, which restrict their validity when applied to the patient setting: no immunosuppressive treatment was given for either GVHD prophylaxis or treatment and no infectious challenges were concurrently performed, both of which will have significant impact on chemokine expression *in vivo*.

In addition, chemokines have currently gained attention as potential biomarkers in the prediction of GVHD, as, for example, shown for CCL8 both in mice and men (Ota et al. 2009; Hori et al. 2008).

A fundamental requirement for the development of aGVHD is the close interaction between host APCs and donor T cells in secondary lymphoid organs. Here, alloantigen gets presented to the T cell, leading to T cell activation, proliferation, and generation of cellular effector cells. The progeny of cellular effectors will leave the lymphoid compartment and infiltrate peripheral aGVHD target organs (Ferrara et al. 2009; Beilhack et al. 2005).

CCR7, which is expressed on dendritic cells, naïve, and central memory T cells, is responsible for the recirculation of these cells into lymphoid organs in response to their ligands CCL19 and CCL21, and therefore is critical to the initiation of GVHD (Forster et al. 2008; Weninger et al. 2001; Yakoub-Agha et al. 2006; Sasaki et al. 2003). Additional chemokines, which are increasingly expressed in secondary lymphoid tissue after allogeneic HSCT, include CCL2-5, CCL8, CCL12, CXCL9-11, and XCL1, and are potentially involved in T cell activation and homing (Choi et al. 2007; New et al. 2002; Wysocki et al. 2004; Bouazzaoui et al. 2009; Serody et al. 2000), although these processes are not yet fully understood.

In this review we will focus primarily on the role of chemokines and their related receptors in the development of aGVHD in peripheral target organs (GI tract, liver, skin, and lung) by using a basic science – clinical comparative approach.

4.1 Chemokines and aGVHD of the Gastrointestinal Tract

Both pathophysiologically and clinically, the GI tract is of particular significance as a target organ of aGVHD. Accordingly, to better understand the mechanisms, regulating intestinal T cell trafficking during homeostasis and inflammation has been of major interest. CCR9 and its ligand CCL25 have been shown to participate in the recruitment of gut-tropic effector cells during homeostasis and inflammation (Saruta et al. 2007; Papadakis et al. 2001; Nishimura et al. 2009; Koenecke and Forster 2009). Hadeiba et al. report on a CCR9+ subset of tolerogenic, plasmacytoid dendritic cells, which migrate to the gut in response to CCL25, display tissue protective properties via the induction of regulatory T cells, and suppress antigen-specific immune responses, including aGVHD (Hadeiba et al. 2008).

An association for CCR5 with the development of aGVHD has been described both clinically and in experimental studies. The presence of the loss of function 32-nucleotide deletion (CCR5Δ32) in patients undergoing allogeneic HSCT resulted in a decreased incidence of aGVHD. Even more important, although the presence of the mutation in only the donor did not seem to alter the development of aGVHD, the presence of CCR5Δ32 genotype in both recipient and donor displayed highest protection, with none of the 11 patients suffering from aGVHD (Bogunia-Kubik et al. 2006). These findings go along with the prior reports on a genetic predisposition of donor or patient being responsible for the development of aGVHD in patients receiving allogeneic HSCT (Holler et al. 2004, 2006; Gruhn et al. 2009; Tseng et al. 2009; Ambruzova et al. 2009a, b; Markey et al. 2008; MacMillan et al. 2003a, b; Takahashi et al. 2000; Middleton et al. 1998).

Protection from GVHD in the absence of functional CCR5 surface expression has also been demonstrated by Murai and colleagues using a murine HSCT model, as they describe an important role for the expression of CCR5 on allogeneic donor T cells for their homing to Peyer's patches. Peyer's patches are an integral part of secondary lymphoid tissue, essentially involved in T cell priming and activation, and therefore, critically contributing to the initiation of aGVHD (Murai et al. 2003). However, in this study, recipient mice were not conditioned, and conflicting data demonstrating an even higher GVHD severity using a model, in which lethally irradiated mice were transplanted with CCR5 defective donor cells, have been reported by Wysocki et al. (Wysocki et al. 2004). The observed contrary outcome was probably due to conditioning regimen-related tissue toxicity, leading to increased proinflammatory chemokine expression in GVHD target organs, and, when compared to CCR5 wild-type cells, due to enhanced migratory properties of murine CCR5−/− T cells towards the CXC chemokine CXCL10, presumably using CXCR3 (Wysocki et al. 2004). Furthermore, lacking CCR5 on donor regulatory T cells (Tregs) may loosen a brake, which normally hinders GVHD propelling, therefore leading to more severe established disease (Wysocki et al. 2005a). In the study by Bouazzaoui et al., expression levels of CCL4 and CCL5, which both share CCR5 as a receptor with CCL3, were not significantly elevated in the GI tract of allogeneic recipients (Bouazzaoui et al. 2009), whereas another study

demonstrated an increase in colonic CCL5 expression on day 6 after HSCT (Mapara et al. 2006). High intestinal expression of CCL3 can be seen early, and most likely sources from the intestinal mucosa itself (Serody et al. 2000). In contrast to CCR5, CCR1 expression was not strongly elevated in the gut early after allogeneic HSCT (Bouazzaoui et al. 2009), suggesting that CCL3 (CCL5): CCR5 interactions rather than CCL4 or CCR1 are involved in early recruitment of T cells to the GI tract, promoting the initiation of aGVHD. However, CCL5:CCR1 interactions seem to indirectly contribute to GVHD target organ injury, as the absence of CCR1 on donor T cells resulted in generally suppressed alloreactive T cell activation, resulting in decreased injury to gut and liver as well (Choi et al. 2007).

Another potential target in the treatment of acute intestinal GVHD is CXCR3. Mapara et al. demonstrated that using myeloablative conditioning regimen by itself is sufficient to induce a significant but partially short-lived increase of CXCR3 ligands, especially CXCL10, in the colon, which was not seen after non-myeloablative conditioning. Subsequent development of aGVHD further increased CXCR3 ligand expression over the first 10 days, thus underlying the importance of Th1 immune responses in this early phase of aGVHD with respect to inflammatory chemokine induction (Mapara et al. 2006). The expression of the CXCR3 ligand family (CXCL9-11) remains elevated throughout the cellular phase of aGVHD (phase 3) (Bouazzaoui et al. 2009). Causal proof for a role of CXCR3 being expressed on CD8+ T cells in the development of intestinal aGVHD has been provided by Duffner et al. In animals transplanted with CD8+ CXCR3−/− donor T cells, T cells expanded and accumulated in the spleen and infiltration of the GI tract was reduced, leading to diminished intestinal GVHD as well as prolonged survival (Duffner et al. 2003). A confirmative study, in which prolonged administration of an anti-CXCR3 neutralizing antibody was successfully used in a mouse model of human GVHD, has been published by He et al. (2008).

Ueha et al. demonstrated a specific role for donor cell expressed CX3CL1 in the recruitment of alloreactive CD8+ T cells into the GI tract after allogeneic HSCT, when administration of an CX3CL1 antibody resulted in decreased numbers of CD8+ T cells in the gut, but did not show any effect on hepatic infiltrates (Ueha et al. 2007).

CCR6 has been implemented into the recruitment of alloreactive CD4+ T cells to GVHD target organs, including the GI tract, liver, and skin, as allogeneic HSCT with CCR6−/− resulted in significantly reduced disease severity (Varona et al. 2005). CCR6 may play a role in both effector and regulatory T cell function (Varona et al. 2006).

The exact role of other chemokines in the development of GI tract GVHD still remains to be defined. CXCR6 expression on CD8+ T cells contributes to the early recruitment of these cells to the liver, but not to the gut, early after allogeneic HSCT (Ueha et al. 2007; Sato et al. 2005). Consistent with these findings, intestinal expression of the CXCR6 ligand, CXCL16, was not increased early after transplantation (Bouazzaoui et al. 2009), and therapeutically, early interventions such as the use of neutralizing antibodies against CXCL16 did not alter the course of intestinal

GVHD (Ueha et al. 2007). However, as CXCL16 expression eventually rises over time (Bouazzaoui et al. 2009), and CXCR6 expression associates with increased T cell numbers in the GI tract, it cannot currently be excluded that CXCR6: CXCL16 interactions potentially contribute to T cell infiltration of the intestine at later time points.

Conflicting data has also been reported on CCR2 and its ligands. While Terwey et al. describe a defect in the migratory capacity of CD8+ CCR2−/− T cells, resulting in reduced infiltration in the gut, this could not confirmed by Hildebrandt and colleagues (Hildebrandt et al. 2004b; Terwey et al. 2005).

4.2 Chemokines and aGVHD of the Liver

The liver presents the second classical target organ of aGVHD. Hepatic GVHD is characterized by endothelial dysfunction, lymphocyte infiltration of the portal areas, and pericholangitis, which ultimately leads to bile duct destruction (Ferrara et al. 2009). Several chemokines and chemokine receptors have been reported to be increasingly expressed: CCL1-5, CCL7, CCL8, CXCL1, CXCL2, CXCL9, CXCL10, CXCL11, CXCL16, XCL1, CCR1, CCR5, CXCR2, CXCR6, and XCR1 (Choi et al. 2007; Mapara et al. 2006; New et al. 2002; Bouazzaoui et al. 2009; Ichiba et al. 2003; Murai et al. 1999), suggesting a central role of these chemokines in attracting alloreactive donor T cells during the course of disease.

In 1999, Murai and colleagues reported as one of the first chemokine receptors involved in GVHD-related liver injury that CCR5 expression on CD8+ T cells plays a substantial role in the hepatic migration of these cells when both the vivo neutralization of the receptor and one of the ligands, CCL3, resulted in significantly decreased T cell infiltration into the liver (Murai et al. 1999). As seen for the GI tract, CCR1, a second receptor for the CCR5 ligands CCL3-5, contributes to hepatic GVHD as well (Choi et al. 2007). However, at this point it is unclear whether the reduction in liver injury in the absence of CCR1 on donor T cells is primarily due to the general suppression of T cell activation or is co-mediated by an impaired migratory capacity in response to CCR1 ligands. Increased CCL3 expression not only derives from hepatic tissue, for example, bile duct epithelial cells and endo-thelial cells, but also from macrophages and infiltrating donor T cells (Serody et al. 2000), suggesting a chemokine-mediated feedback mechanism on the recruitment of CCR1+ and CCR5+ donor T cells to the liver. In contrast, Wysocki et al. showed an accumulation of CCR5 deficient T cells in the liver following allogeneic HSCT, as well as a higher sensitivity of these cells to CXCR3 ligands was postulated. As at the same time liver histopathology was not increased, the authors speculated that the cells were rather being trapped by the sinusoidal epithelium than directly causing tissue damage (Wysocki et al. 2004).

Redundancy of function of the chemokine–chemokine receptor system provides evolutionary stability. Correspondingly, CD8+ T cells infiltrate the sites of inflam-mation in hepatic GVHD not only using CCR5 or CCR1 but also other chemokine

receptors, such as CXCR3 and CXCR6. Transplantation of allogeneic CXCR3−/− donor T cells or the use of anti-CXCR3 antibodies resulted in decreased hepatic injury (Duffner et al. 2003; He et al. 2008), and Sato et al. described a markedly reduced migratory capacity of CXCR6−/− CD8+ but not CD4+ T cells to the liver following allogeneic HSCT (Sato et al. 2005). Furthermore, the latter study was confirmed targeting CXCL16, the ligand of CXCR6, when administration of anti-CXCL16 antibodies led to a reduction in liver tissue damage (Ueha et al. 2007).

Terwey et al. reported the contribution of CCR2 on donor cells to CD8+ T cell-mediated hepatic aGVHD (Terwey et al. 2005), whereas in CD4+ T cell-mediated hepatic aGVHD, CCR2 deficiency of donor T cells rather led to increased T cell infiltrates (Rao et al. 2003), and when using a CD4+ and CD8+ T cell-mediated GVHD model, no significant effect of donor cell CCR2 deficiency on liver histopathology was found (Hildebrandt et al. 2004b).

4.3   Chemokines and aGVHD of the Skin

One of the most frequent sites of aGVHD is the skin (Goker et al. 2001; Ferrara et al. 2009; Breathnach and Katz 1987), usually preceding intestinal or hepatic involvement. Both experimental and clinical studies indicate an increased cutaneous expression of a number of chemokines and their receptors following allogeneic HSCT. Specifically, in murine studies, which are usually performed without immunosuppressive GVHD prophylaxis or treatment, elevated expression levels peaked rather early after transplantation within the first two weeks as shown for CXCL1, CXCL2, CXCL9-11, CCL2, CCL5-9, CCL11, CCL12, CCL19, and XCL1, correlating with some of their respective receptors, including CCR1, CCR5, CXCR3, and XCR1 (Mapara et al. 2006; Sugerman et al. 2004; Bouazzaoui et al. 2009). CCR2 expression was significantly induced by week 3, and CXCR3 demonstrated a second peak during the late cellular cytotoxic phase of aGVHD (phase 3) at week 6 after HSCT (Bouazzaoui et al. 2009). Clinically, the infiltration of CD4+ CCR10+ CCR7low CCR4+ CXCR3+ CCR6− T cells into GVHD skin correlated with increased epidermal expression of CCL27 (Faaij et al. 2006). Interestingly, this T cell population was not found in the GI tract of a (although limited) number of four patients with intestinal aGVHD, suggesting that CCR10–CCL27 interactions may be specifically relevant for tissue-specific migration of alloreactive T cells to the skin during aGVHD (Faaij et al. 2006; Reiss et al. 2001). CCR10 was not found on skin infiltrating CD8+ T cells in patients with cutaneous GVHD (Faaij et al. 2006), and other chemokine receptors such as CXCR3 may be predominantly responsible for CD8+ T cell recruitment to the skin (He et al. 2008; Flier et al. 2001). Piper et al. reported an association between CXCR3+ lymphocytes with one of its ligand, CXCL10, in biopsies of patients with skin GVHD, but not explicitly looked at CD4+ vs. CD8+ T cell subsets (Piper et al. 2007). Other chemokine receptors potentially involved in regulating the recruitment of T cells

into inflamed skin during GVHD are CCR5 (Morita et al. 2007; Palmer et al. 2009) or CCR9 (Inamoto et al. 2009).

A better understanding, why not every patient undergoing allogeneic HSCT develops cutaneous GVHD, may be deducted from the study by Inamoto et al., who demonstrated that the presence of the nonsynonymous single nucleotide polymorphism of CCR9 gene (926AG) in the donor substantially increases the risk to specifically develop GVHD target organ injury to the skin (Inamoto et al. 2009).

Langerhans cells are the major APC in the skin and substantially involved in the pathophysiology of cutaneous GVHD (Merad et al. 2002, 2004). Merad and co-workers elegantly showed that host Langerhans cells are critical to propel skin injury following allogeneic HSCT. Host Langerhans cells can persist for several months within the skin and can be responsible for the onset of skin GVHD at later time points. Alloreactive T cells infiltrating the skin deplete host Langerhans cells, induce the expression of CCL2 and CCL20, which are the ligands for Langerhans cell-expressed CCR2 and CCR6, respectively, and – predominantly using CCR6: CCL20 interactions, facilitated by CCR2:CCL2 – promote the recruitment of donor Langerhans cells into the skin (Merad et al. 2002, 2004). Consistently, in a clinical study on Langerhans cell chimerism in eight children undergoing allogeneic HSCT, Emile et al. reported that, in the two patients receiving a T cell-depleted transplant, no donor Langerhans cells were present in the skin, whereas in patients receiving a non-T cell-depleted transplant, donor Langerhans cells could be found (Emile et al. 1997).

4.4 Chemokines and aGVHD of the Lung

Acute noninfectious diffuse lung injury, classically defined as idiopathic pneumonia syndrome (IPS), has been associated with mortality rates of >70% (Clark et al. 1993; Kantrow et al. 1997) and has an incidence between 5 and 25% (Clark et al. 1993; Kantrow et al. 1997; Crawford and Hackman 1993; Crawford et al. 1993; Krowka et al. 1985; Weiner et al. 1986). IPS has not been traditionally considered as a form of aGVHD of the lung. However, over the last years, growing evidence indicates that alloreactive immune responses are involved (Cooke et al. 1998; Miklos et al. 2008; Kraetzel et al. 2008), leading to the concept of IPS as a form of pulmonary graft vs. host disease (pGVHD) (Miklos et al. 2008).

As infiltration of the lung by donor T cells, monocytes, and macrophages is a characteristic hallmark (Hildebrandt et al. 2004a; Cooke et al. 1998; Clark et al. 1998; Panoskaltsis-Mortari et al. 1997, 2001; Cooke et al. 2000), several studies investigated the role of chemokines both with respect to their expression levels and their mechanistic function in order to better understand the underlying mechanisms of leukocyte recruitment (Hildebrandt et al. 2004a, b, c, 2005; Wysocki et al. 2004; Serody et al. 2000; Panoskaltsis-Mortari et al. 2000, 2003). Several pro-inflammatory chemokines (CCL2, CCL3-5, CXCL9-11, XCL1, CCL2, CCL8, CCL12, and

CXCL1) and chemokine receptors (CXCR3, CCR1, CCR2, CCR5, CXCR6, and XCR1) are increasingly expressed during the development of acute pGVHD (Hildebrandt et al. 2004a, b, c, 2005; Serody et al. 2000; Panoskaltsis-Mortari et al. 2000; Hildebrandt et al. 2003, 2008). Functional studies have further revealed the relevance of a number of specific chemokine ligand–chemokine receptor interactions (Hildebrandt et al. 2004a, b, 2005; Serody et al. 2000; Panoskaltsis-Mortari et al. 2003) by either using genetically engineered ligand-/receptor-deficient animals or the *in vivo* administration of neutralizing antibodies.

Early after HSCT, increased expression of CXCL9 and CXCL10 was associated with the recruitment of CXCR3+ T cells into the lung (Hildebrandt et al. 2004a). In this study, both the use of CXCR3−/− donor cells as well as the use of anti-CXCL9 or anti-CXCL10 antibodies resulted in decreased T cell numbers in the lung, and subsequently in reduced lung injury. Interestingly, while isolated *in vivo* neutralization of either CXCL9 or CXCL10 partially reduced pulmonary infiltrates, an additive effect could be observed when both ligands were targeted simultaneously (Hildebrandt et al. 2004a). T cell-derived chemokines (CCL3, CCL5) and cytokines, for example, TNF, directly or indirectly through enhanced tissue injury and chemokine induction mediate the recruitment of CCR2+ monocytes and macrophages into the lung (Hildebrandt et al. 2003, 2004b, 2005; Cooke et al. 1998; Serody et al. 2000), which themselves contribute to pulmonary injury through the production of TNF (Hildebrandt et al. 2004c). Migration of donor monocytes/macrophages seems critically regulated through the increased pulmonary expression of the chemokine ligand CCL2, as both immunoneutralization of CCL2 and the absence of CCR2 on donor cells resulted in decreased inflammatory infiltrates and reduction in lung injury (Hildebrandt et al. 2004b), while CCR2 expression on host cells did not matter (Panoskaltsis-Mortari et al. 2004). A regulatory loop on leukocyte migration to the lung has additionally been characterized, as donor T cells through the production of inflammatory chemokines, such as CCL3 and CCL5, can promote subsequent T cell recruitment and propel the severity of disease (Hildebrandt et al. 2005; Serody et al. 2000), although for CCL3 this is not absolutely clear (Panoskaltsis-Mortari et al. 2003). These cascading events in the progression of acute pGVHD exemplify chemokines as critical mediators and potential therapeutic targets in this disease, and led Miklos et al. to the assumption that broad spectrum chemokine inhibition may prove efficient particularly in this disease (Miklos et al. 2009). Grainger et al. have developed a series of oligopeptides that act as functional chemokine inhibitors (Grainger and Reckless 2003). One of these oligopeptides is the broad spectrum chemokine inhibitor (BSCI) NR58-3.14.3, an anti-inflammatory agent, which suppresses the *in vitro* and *in vivo* migration of leucocytes in response to several chemokines, including CCL2, CXCL8 (IL-8), CCL3, and CCL5 (Reckless et al. 2001). Treating mice with this BSCI over the first 2 weeks following allogeneic HSCT resulted in improved pulmonary function and decreased pGVHD severity as well as in a minor reduction in hepatic GVHD, but did not affect intestinal GVHD (Miklos et al. 2009).

5 The Role of the Chemokine–Chemokine Receptor System in cGVHD

Studies on chemokines and chemokine receptors in cGVHD are limited. This may be due to various reasons, including the lack of a standardized classification system, which incorporates the variety of organs and symptoms involved, and the lack of a "one fits all" mouse model of cGVHD. While the former has been recently approached by the National Institute of Health Consensus Development Project on cGVHD (Filipovich et al. 2005; Pavletic et al. 2006a, b), the latter still remains a scientific challenge.

Clinically, a retrospective patient study carried out by Kim et al. described single nucleotide polymorphisms (SNPs) in the CCL5 promoter gene of HSCT recipients to be associated with a higher incidence and severity of cGVHD (Kim et al. 2007). Correspondingly, Morita et al. suggested a role for CCR5 expression on lymphocytes in the development of cGVHD of the skin (Morita et al. 2007).

Up to date, there are three major mouse models dealing with different aspects of cGVHD, involving autoantibody production, fibrosis, and thymic dysfunction. CD4+ T cell activation, resulting in B cell stimulation, and the production of autoantibodies are the main features of a so-called SLE-cGVHD model. The adoptive transfer of MHC mismatched, mature immune cells into a nonirradiated host leads to the generation of DNA-specific autoantibodies and immune-complex glomerulonephritis, both are characteristic findings in human systemic lupus erythematosus (SLE), but are rather infrequently seen in patients with cGVHD. Therefore, this model does not seem to be ideally suited for mimicking human cGVHD, and its validity maybe limited to specific pathophysiological aspects (Martin 2008; Chu and Gress 2008).

Unquestionable fibrosis of the skin and of different other organs is one of the key pathological mechanisms of chronic disease, which is reflected in the sclerodermatous (Scl)-cGVHD model. In this model, irradiated BALB/c (H-2^d) mice are transplanted with bone marrow and splenocytes from minor histocompatibility loci different B10.D2 (H-2^d) donors, resulting in fibrosis of skin, liver, lung, GI tract, and salivary glands. Zhou et al. analyzed mRNA expression levels of chemokines and chemokine receptors in the skin of Scl-cGVHD mice on d7, d30, d60, and d120 after HSCT (Zhou et al. 2007). Measurable skin thickening occurred after 3–5 weeks, and cytokine expression revealed a mixed Th1/Th2 profile with a shift towards a Th2 predominance during the course of skin fibrosis. Consistent with prior findings in mice and human scleroderma (Derk and Jimenez 2003; Zhang et al. 2002), upregulated chemokines included CCL2, CCL3, CCL5, and CCL7. Other chemokines increasingly expressed were the Th1-associated IFNγ-inducible chemokines CXCL9-11 and the Th2-associated chemokines CCL17 and CCL22. CCL17 is involved in the recruitment of CCR4+ lymphocytes to inflamed skin (Reiss et al. 2001). Elevated levels of CCL2, CCL17, and CCL22 were also found in the bronchoalveolar fluid of patients with idiopathic pulmonary fibrosis (IPF) and were predictive of poor outcome. Interestingly, relative and absolute numbers of

macrophages, lymphocytes, neutrophils, and eosinophils in that study did not differ between survivors and nonsurvivors. Likewise, the CD4+/CD8+ ratio was not different (Shinoda et al. 2009). CCL2 is able to induce collagen and TGF-β gene expression in fibroblasts, consistent with elevated TGF-β levels found at later stages in the murine Scl-cGVHD model (Zhang et al. 2002). CXCL9-11 were increased in accordance with the elevated expression of IFNγ noted during early fibrosis and the upregulation of both Th1- and Th2-associated chemokines points to a more complex pathophysiology involving both Th1 and Th2 mechanisms (Zhou et al. 2007).

The third experimental model focuses on the observed thymic dysfunction following allogeneic HSCT, and may help to explain the differences in cGVHD incidence between pediatric and adult patients. Sakoda et al. were able to show that impaired negative selection in the thymus results in the generation of autoreactive T cells, which can cause clinical cGVHD in mice resembling numerous features of human cGVHD (Sakoda et al. 2007). However, further studies employing this model are still pending.

Late onset noninfectious pulmonary complications can present both with restrictive lung function impairment [restrictive pulmonary function test (PFT) pattern, late interstitial pneumonitis (IP), and cryptogenic organizing pneumonia (COP)], air outflow obstruction [obstructive PFT pattern, obliterative bronchiolitis (BO), and bronchiolitis obliterans syndrome (BOS)], or a combination of both (Cooke and Hildebrandt 2006; Tichelli et al. 2008; Bolanos-Meade and Chien 2009). These forms of pulmonary disease are strongly associated with cGvHD and therefore, although not pathophysiologically fully understood, are being considered potential forms of pulmonary cGVHD (Cooke and Hildebrandt 2006; Tichelli et al. 2008; Bolanos-Meade and Chien 2009; Patriarca et al. 2004; Sakaida et al. 2003; Savani et al. 2006; Nishio et al. 2009; Freudenberger et al. 2003; Uderzo et al. 2007). A murine model of BO following allogeneic HSCT has been lacking until recently when Panoskaltsis-Mortari et al. demonstrated the development of obliterative changes in lungs of allogeneic recipients along with increasing levels of CXCL1 (human CXCL8) (Panoskaltsis-Mortari et al. 2007). While no functional study with respect to chemokines and their receptors in the development of BO after HSCT has yet been reported, other groups have shown the critical contribution of CCR2, CXCR2, and CXCR3 together with their respective ligands in the pathophysiology of BO after lung transplantation (Belperio et al. 2001, 2002, 2003, 2005), which may play a role following HSCT as well.

6 Current Possibilities and Perspectives for Targeting the Chemokine–Chemokine Receptor System in GVHD

Besides their described role in GVHD, chemokine and chemokine receptor expression and interactions are importantly involved in various diseases, for example, autoimmune diseases and HIV infection. For example, CCR5 is well known for

their pivotal role in HIV entry into the cell. Therefore, small molecules targeting these receptors have been a focus in the development of new treatment modalities, which resulted in the discovery of maraviroc, up-to-date the only CCR5 antagonist commercially available and FDA-approved for HIV therapy (Lieberman-Blum et al. 2008). As outlined in this review article, CCR5 and its ligands seem to play an integral role in the recruitment of effector T cells to GVHD organs, and targeting this receptor may present a promising alternative approach for disease modulation and therapy. However, it has to be kept in mind that, in one study, CCR5 deficiency of Tregs resulted in exaggerated GVHD severity (Wysocki et al. 2005a). Responses to treatment approaches targeting specific chemokines or chemokine receptors, therefore, may not be as uniform as expected, as functional relevance of the targeted structure may be distributed across different systems, and therefore, potentially contrary effects can occur.

Considering the importance of Th1-based inflammatory responses during early aGVHD and the relevance of increased CXCR3 ligand expression on the recruitment of alloreactive CXCR3+ donor T cells to GVHD target organs (Duffner et al. 2003; Hildebrandt et al. 2004a; He et al. 2008), CXCR3 presents another interesting target. Several patents for CXCR3 antagonists were already disclosed, but none has yet been approved for clinical use (Pease and Horuk 2009).

CCR9 has been recently identified as a critical homing-receptor for lymphocytes involved in GI inflammation like Crohn's disease (Saruta et al. 2007). With CCX282 an orally bioactive inhibitor has been designed, which is currently being tested in phase III clinical trials (Pease and Horuk 2009), and – depending on the results – may provide a promising approach in the treatment of intestinal GVHD as well.

As reviewed in this article, CCR5, CXCR3, and CCR9 present only a few of the potential targets among others (e.g., CCR2, CXCR6, CCL2, CCL3, CCL5, and CXCL16) within the chemokine–chemokine receptor system, for which selective neutralization or specific blockade through newly developed antibodies or small molecules seems to be indicated in future. However, the successful translation from bench to bedside may be hampered by the complexity, the redundancy, and the pleiotropy of the chemokine system. In addition, experimental data from models using chemokine receptor knock out animals have been somewhat controversial [e.g., CCR2 (Terwey et al. 2005) vs. (Hildebrandt et al. 2004b); CCR5 (Murai et al. 2003) vs. (Wysocki et al. 2004)]. The observed discrepancy may reflect mouse strain-dependent and conditioning regimen- or T cell dose-related characteristics, but it also suggests that, while blocking one single receptor or ligand, disease activity and progression are maintained, mediated through alternative chemokine–chemokine-receptor interactions (Wysocki et al. 2004), which either simply take over function or are even compensatory upregulated.

One way to overcome this problem could be the use of promiscuous antagonists, that is, agents, which inhibit the binding capacity or the intracellular signaling pathways of two or more receptors at the same time (Pease and Horuk 2009). Recently developed oligopeptides may fall under this category, as they act as functional chemokine inhibitors (Grainger and Reckless 2003; Fox et al. 2009),

and one member of this group of broad spectrum chemokine inhibitors, NR58-3.14.3, has been successfully tested in murine GVHD, reducing target organ injury to the lung and to the liver (Miklos et al. 2009).

Another novel and very interesting approach to treat aGVHD has been suggested by Hasegawa et al. (2008). They took advantage of the pathologic overexpression of CXCR3 ligands in GVHD target organs by using it as chemotactic signal for CXCR3-transfected Tregs, resulting in targeted delivery of these cells to GVHD target organs and in a reduction in GVHD severity (Hasegawa et al. 2008). Similar approaches being applied to other chemokine receptors may prove beneficial as well, as using this scenario, Treg-mediated immunosuppresion may rather be locally confined than systemically relevant.

Caveats of any modulation of immune responses, including the usage of specific chemokine or chemokine receptor blocking agents, the use of broad spectrum chemokine inhibitors, the application of Tregs or any other kind of immunosuppression, include the potential increase in susceptibility to infection and a potential loss of GVL. These issues have been insufficiently addressed in experimental studies so far and further clarifying studies are needed.

References

Addison CL, Daniel TO, Burdick MD, Liu H, Ehlert JE, Xue YY et al (2000) The CXC chemokine receptor 2, CXCR2, is the putative receptor for ELR + CXC chemokine-induced angiogenic activity. J Immunol 165(9):5269–5277

Allen SJ, Crown SE, Handel TM (2007) Chemokine: receptor structure, interactions, and antagonism. Annu Rev Immunol 25:787–820

Ambruzova Z, Mrazek F, Raida L, Jindra P, Vidan-Jeras B, Faber E et al (2009a) Association of IL6 and CCL2 gene polymorphisms with the outcome of allogeneic haematopoietic stem cell transplantation. Bone Marrow Transplant 44(4):227–235

Ambruzova Z, Mrazek F, Raida L, Stahelova A, Faber E, Indrak K et al (2009b) Possible impact of MADCAM1 gene single nucleotide polymorphisms to the outcome of allogeneic hematopoietic stem cell transplantation. Hum Immunol 70(6):457–460

Baird K, Pavletic SZ (2006) Chronic graft versus host disease. Curr Opin Hematol 13(6):426–435

Barrett AJ (1997) Mechanisms of the graft-versus-leukemia reaction. Stem Cells 15(4):248–258

Beilhack A, Schulz S, Baker J, Beilhack GF, Wieland CB, Herman EI et al (2005) *In vivo* analyses of early events in acute graft-versus-host disease reveal sequential infiltration of T-cell subsets. Blood 106(3):1113–1122

Belperio JA, Keane MP, Arenberg DA, Addison CL, Ehlert JE, Burdick MD et al (2000) CXC chemokines in angiogenesis. J Leukoc Biol 68(1):1–8

Belperio JA, Keane MP, Burdick MD, Lynch JP 3rd, Xue YY, Berlin A et al (2001) Critical role for the chemokine MCP-1/CCR2 in the pathogenesis of bronchiolitis obliterans syndrome. J Clin Invest 108(4):547–556

Belperio JA, Keane MP, Burdick MD, Lynch JP 3rd, Xue YY, Li K et al (2002) Critical role for CXCR3 chemokine biology in the pathogenesis of bronchiolitis obliterans syndrome. J Immunol 169(2):1037–1049

Belperio JA, Keane MP, Burdick MD, Lynch JP 3rd, Zisman DA, Xue YY et al (2003) Role of CXCL9/CXCR3 chemokine biology during pathogenesis of acute lung allograft rejection. J Immunol 171(9):4844–4852

Belperio JA, Keane MP, Burdick MD, Gomperts B, Xue YY, Hong K et al (2005) Role of CXCR2/CXCR2 ligands in vascular remodeling during bronchiolitis obliterans syndrome. J Clin Invest 115(5):1150–1162

Bogunia-Kubik K, Duda D, Suchnicki K, Lange A (2006) CCR5 deletion mutation and its association with the risk of developing acute graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Haematologica 91(12):1628–1634

Bolanos-Meade J, Chien J (2009) Chronic graft-versus-host disease and the lung. In: Vogelsang GB, Pavletic SZ (eds) Chronic graft-versus-host disease. Cambridge University Press, UK, pp 229–237

Bouazzaoui A, Spacenko E, Mueller G, Miklos S, Huber E, Holler E et al (2009) Chemokine and chemokine receptor expression analysis in target organs of acute graft-versus-host disease. Genes Immun 10(8):687–701

Breathnach SM, Katz SI (1987) Immunopathology of cutaneous graft-versus-host disease. Am J Dermatopathol 9(4):343–348

Broxmeyer HE (2008) Chemokines in hematopoiesis. Curr Opin Hematol 15(1):49–58

Cahn JY, Klein JP, Lee SJ, Milpied N, Blaise D, Antin JH et al (2005) Prospective evaluation of 2 acute graft-versus-host (GVHD) grading systems: a joint Societe Francaise de Greffe de Moelle et Therapie Cellulaire (SFGM-TC), Dana Farber Cancer Institute (DFCI), and International Bone Marrow Transplant Registry (IBMTR) prospective study. Blood 106(4):1495–1500

Campbell JJ, Hedrick J, Zlotnik A, Siani MA, Thompson DA, Butcher EC (1998) Chemokines and the arrest of lymphocytes rolling under flow conditions. Science 279(5349):381–384

Champlin RE, Schmitz N, Horowitz MM, Chapuis B, Chopra R, Cornelissen JJ et al (2000) Blood stem cells compared with bone marrow as a source of hematopoietic cells for allogeneic transplantation. IBMTR Histocompatibility and Stem Cell Sources Working Committee and the European Group for Blood and Marrow Transplantation (EBMT). Blood 95(12):3702–3709

Choi SW, Hildebrandt GC, Olkiewicz KM, Hanauer DA, Chaudhary MN, Silva IA et al (2007) CCR1/CCL5 (RANTES) receptor-ligand interactions modulate allogeneic T-cell responses and graft-versus-host disease following stem-cell transplantation. Blood 110(9):3447–3455

Chu YW, Gress RE (2008) Murine models of chronic graft-versus-host disease: insights and unresolved issues. Biol Blood Marrow Transplant 14(4):365–378

Clark J, Hansen J, Hertz M, Parkman R, Jensen L, Peavy H (1993) Idiopathic pneumonia syndrome after bone marrow transplantation. Am Rev Respir Dis 147:1601–1606

Clark JG, Madtes DK, Hackman RC, Chen W, Cheever MA, Martin PJ (1998) Lung injury induced by alloreactive Th1 cells is characterized by host-derived mononuclear cell inflammation and activation of alveolar macrophages. J Immunol 161:1913–1920

Constantin G, Majeed M, Giagulli C, Piccio L, Kim JY, Butcher EC et al (2000) Chemokines trigger immediate beta2 integrin affinity and mobility changes: differential regulation and roles in lymphocyte arrest under flow. Immunity 13(6):759–769

Cooke KR, Hildebrandt GC (2006) Pulmonary toxicity following hematopoietic cell transplantation: Is the lung a target organ of graft-versus-host disease? Curr Opin Organ Transplant 11(1):69–77

Cooke KR, Krenger W, Hill G, Martin TR, Kobzik L, Brewer J et al (1998) Host reactive donor T cells are associated with lung injury after experimental allogeneic bone marrow transplantation. Blood 92(7):2571–2580

Cooke KR, Hill GR, Gerbitz A, Kobzik L, Martin TR, Crawford JM et al (2000) Hyporesponsiveness of donor cells to lipopolysaccharide stimulation reduces the severity of experimental idiopathic pneumonia syndrome: potential role for a gut-lung axis of inflammation. J Immunol 165(11):6612–6619

Crawford S, Hackman R (1993) Clinical course of idiopathic pneumonia after bone marrow transplantation. Am Rev Respir Dis 147:1393

Crawford S, Longton G, Storb R (1993) Acute graft-versus-host disease and the risks for idiopathic pneumonia after marrow transplantation for severe aplastic anemia. Bone Marrow Transplant 12:225

Cutler C, Giri S, Jeyapalan S, Paniagua D, Viswanathan A, Antin JH (2001) Acute and chronic graft-versus-host disease after allogeneic peripheral-blood stem-cell and bone marrow transplantation: a meta-analysis. J Clin Oncol 19(16):3685–3691

Czermak BJ, Sarma V, Bless NM, Schmal H, Friedl HP, Ward PA (1999) *In vitro* and *in vivo* dependency of chemokine generation on C5a and TNF-alpha. J Immunol 162(4):2321–2325

Datta AR, Barrett AJ, Jiang YZ, Guimaraes A, Mavroudis DA (1994) Distant T cell populations distinguish chronic myeloid leulaemia cells from lymphocytes in the same individual: a model for separating GVHD from GVL reactions. Bone Marrow Transplant 14:517–524

Derk CT, Jimenez SA (2003) Systemic sclerosis: current views of its pathogenesis. Autoimmun Rev 2(4):181–191

Duffner U, Lu B, Hildebrandt GC, Teshima T, Williams DL, Reddy P et al (2003) Role of CXCR3-induced donor T-cell migration in acute GVHD. Exp Hematol 31(10):897–902

Emile JF, Haddad E, Fraitag S, Canioni D, Fischer A, Brousse N (1997) Detection of donor-derived Langerhans cells in MHC class II immunodeficient patients after allogeneic bone marrow transplantation. Br J Haematol 98(2):480–484

Faaij CM, Lankester AC, Spierings E, Hoogeboom M, Bowman EP, Bierings M et al (2006) A possible role for CCL27/CTACK-CCR10 interaction in recruiting CD4 T cells to skin in human graft-versus-host disease. Br J Haematol 133(5):538–549

Ferrara JL, Levine JE, Reddy P, Holler E (2009) Graft-versus-host disease. Lancet 373 (9674):1550–1561

Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ et al (2005) National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant 11(12):945–956

Flier J, Boorsma DM, van Beek PJ, Nieboer C, Stoof TJ, Willemze R et al (2001) Differential expression of CXCR3 targeting chemokines CXCL10, CXCL9, and CXCL11 in different types of skin inflammation. J Pathol 194(4):398–405

Forster R, Davalos-Misslitz AC, Rot A (2008) CCR7 and its ligands: balancing immunity and tolerance. Nat Rev 8(5):362–371

Fowler DH, Gress RE (2000) Th2 and Tc2 cells in the regulation of GVHD, GVL, and graft rejection: considerations for the allogeneic transplantation therapy of leukemia and lymphoma. Leuk Lymphoma 38(3–4):221–234

Fowler DH, Breglio J, Nagel G, Eckhaus MA, Gress RE (1996) Allospecific CD8+ Tc1 and Tc2 populations in GVL and GVHD. J Immunol 157:4811

Fowler DH, Breglio J, Nagel G, Gress RE (1997) Allospecific CD4+ Th1/Th2 and CD8+ Tc1/Tc2 populations in murine GVL: type I cells generate GVL, type II cells abrogate GVL. Biol Blood Marrow Transplant 2:118

Fox DJ, Reckless J, Lingard H, Warren S, Grainger DJ (2009) Highly potent, orally available anti-inflammatory broad-spectrum chemokine inhibitors. J Med Chem 52(11):3591–3595

Freudenberger TD, Madtes DK, Curtis JR, Cummings P, Storer BE, Hackman RC (2003) Association between acute and chronic graft-versus-host disease and bronchiolitis obliterans organizing pneumonia in recipients of hematopoietic stem cell transplants. Blood 102 (10):3822–3828

Goker H, Haznedaroglu IC, Chao NJ (2001) Acute graft-vs-host disease: pathobiology and management. Exp Hematol 29(3):259–277

Goulmy E, Schipper R, Pool J, Blokland E, Falkenburg F (1996) Mismatches of minor histocompatibility antigens between HLA-identical donors and recipients and the development of graft-versus-host disease after bone marrow transplantation. N Engl J Med 334(5): 281–285

Grainger DJ, Reckless J (2003) Broad-spectrum chemokine inhibitors (BSCIs) and their anti-inflammatory effects *in vivo*. Biochem Pharmacol 65(7):1027–1034

Gruhn B, Intek J, Pfaffendorf N, Zell R, Corbacioglu S, Zintl F et al (2009) Polymorphism of interleukin-23 receptor gene but not of NOD2/CARD15 is associated with graft-versus-host disease after hematopoietic stem cell transplantation in children. Biol Blood Marrow Transplant 15(12):1571–1577

Hadeiba H, Sato T, Habtezion A, Oderup C, Pan J, Butcher EC (2008) CCR9 expression defines tolerogenic plasmacytoid dendritic cells able to suppress acute graft-versus-host disease. Nat Immunol 9(11):1253–1260

Hancock WW, Lu B, Gao W, Csizmadia V, Faia K, King JA et al (2000) Requirement of the chemokine receptor CXCR3 for acute allograft rejection. J Exp Med 192(10):1515–1520

Hasegawa H, Inoue A, Kohno M, Lei J, Miyazaki T, Yoshie O et al (2008) Therapeutic effect of CXCR3-expressing regulatory T cells on liver, lung and intestinal damages in a murine acute GVHD model. Gene Ther 15(3):171–182

He S, Cao Q, Qiu Y, Mi J, Zhang JZ, Jin M et al (2008) A new approach to the blocking of alloreactive T cell-mediated graft-versus-host disease by *in vivo* administration of anti-CXCR3 neutralizing antibody. J Immunol 181(11):7581–7592

Higman MA, Vogelsang GB (2004) Chronic graft-versus-host disease. Br J Haematol 125(4):435–454

Hildebrandt GC, Olkiewitz KO, Corrion LA, Chang Y, Liu C, Ferrara JLM et al (2003) Secretion of TNF-alpha by donor effector cells is critical in the development of Idiopathic Pneumonia Syndrome after allogeneic stem cell transplantation. Blood 102(11):3529

Hildebrandt GC, Corrion LA, Olkiewicz KM, Lu B, Lowler K, Duffner UA et al (2004a) Blockade of CXCR3 receptor:ligand interactions reduces leukocyte recruitment to the lung and the severity of experimental idiopathic pneumonia syndrome. J Immunol 173(3):2050–2059

Hildebrandt GC, Duffner UA, Olkiewicz KM, Corrion LA, Willmarth NE, Williams DL et al (2004b) A critical role for CCR2/MCP-1 interactions in the development of idiopathic pneumonia syndrome after allogeneic bone marrow transplantation. Blood 103(6):2417–2426

Hildebrandt GC, Olkiewicz KM, Corrion LA, Chang Y, Clouthier SG, Liu C et al (2004c) Donor-derived TNF-alpha regulates pulmonary chemokine expression and the development of idiopathic pneumonia syndrome after allogeneic bone marrow transplantation. Blood 104(2):586–593

Hildebrandt GC, Olkiewicz KM, Choi S, Corrion LA, Clouthier SG, Liu C et al (2005) Donor T-cell production of RANTES significantly contributes to the development of idiopathic pneumonia syndrome after allogeneic stem cell transplantation. Blood 105(6):2249–2257

Hildebrandt GC, Olkiewicz KM, Corrion L, Clouthier SG, Pierce EM, Liu C et al (2008) A role for TNF receptor type II in leukocyte infiltration into the lung during experimental idiopathic pneumonia syndrome. Biol Blood Marrow Transplant 14(4):385–396

Hill GR, Crawford JM, Cooke KR, Brinson YS, Pan L, Ferrara JL (1997) Total body irradiation and acute graft-versus-host disease: the role of gastrointestinal damage and inflammatory cytokines. Blood 90(8):3204–3213

Holler E, Rogler G, Herfarth H, Brenmoehl J, Wild PJ, Hahn J et al (2004) Both donor and recipient NOD2/CARD15 mutations associate with transplant-related mortality and GvHD following allogeneic stem cell transplantation. Blood 104(3):889–894

Holler E, Rogler G, Brenmoehl J, Hahn J, Herfarth H, Greinix H et al (2006) Prognostic significance of NOD2/CARD15 variants in HLA-identical sibling hematopoietic stem cell transplantation: effect on long-term outcome is confirmed in 2 independent cohorts and may be modulated by the type of gastrointestinal decontamination. Blood 107(10):4189–4193

Hori T, Naishiro Y, Sohma H, Suzuki N, Hatakeyama N, Yamamoto M et al (2008) CCL8 is a potential molecular candidate for the diagnosis of graft-versus-host disease. Blood 111(8):4403–4412

Ichiba T, Teshima T, Kuick R, Misek DE, Liu C, Takada Y et al (2003) Early changes in gene expression profiles of hepatic GVHD uncovered by oligonucleotide microarrays. Blood 102(2):763–771

Inamoto Y, Murata M, Katsumi A, Kuwatsuka Y, Tsujimura A, Ishikawa Y et al (2009) Donor single nucleotide polymorphism in the CCR9 gene affects the incidence of skin GVHD. Bone Marrow Transplant 45(2):363–369

Jaksch M, Remberger M, Mattsson J (2005) Increased gene expression of chemokine receptors is correlated with acute graft-versus-host disease after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 11(4):280–287

Kantrow SP, Hackman RC, Boeckh M, Myerson D, Crawford SW (1997) Idiopathic pneumonia syndrome: Changing spectrum of lung injury after marrow transplantation. Transplantation 63 (8):1079–1086

Kaplan DH, Anderson BE, McNiff JM, Jain D, Shlomchik MJ, Shlomchik WD (2004) Target antigens determine graft-versus-host disease phenotype. J Immunol 173(9):5467–5475

Kataoka Y, Iwasaki T, Kuroiwa T, Seto Y, Iwata N, Hashimoto N et al (2001) The role of donor T cells for target organ injuries in acute and chronic graft-versus-host disease. Immunology 103 (3):310–318

Kim DH, Jung HD, Lee NY, Sohn SK (2007) Single nucleotide polymorphism of CC chemokine ligand 5 promoter gene in recipients may predict the risk of chronic graft-versus-host disease and its severity after allogeneic transplantation. Transplantation 84(7):917–925

Koenecke C, Forster R (2009) CCR9 and inflammatory bowel disease. Expert Opin Ther Targets 13(3):297–306

Kolb HJ, Schmid C, Barrett AJ, Schendel DJ (2003) Graft-versus-leukemia reactions in allogeneic chimeras. Blood 103(3):767–776

Kraetzel K, Stoelcker B, Eissner G, Multhoff G, Pfeifer M, Holler E et al (2008) NKG2D-dependent effector function of bronchial epithelium-activated alloreactive T-cells. Eur Respir J 32(3):563–570

Krowka MJ, Rosenow EC 3rd, Hoagland HC (1985) Pulmonary complications of bone marrow transplantation. Chest 87(2):237–246

Lee SJ (2005) New approaches for preventing and treating chronic graft-versus-host disease. Blood 105(11):4200–4206

Lieberman-Blum SS, Fung HB, Bandres JC (2008) Maraviroc: a CCR5-receptor antagonist for the treatment of HIV-1 infection. Clin Ther 30(7):1228–1250

Mackay CR (2001) Chemokines: immunology's high impact factors. Nat Immunol 2(2):95–101

MacMillan ML, Radloff GA, DeFor TE, Weisdorf DJ, Davies SM (2003a) Interleukin-1 genotype and outcome of unrelated donor bone marrow transplantation. Br J Haematol 121(4):597–604

MacMillan ML, Radloff GA, Kiffmeyer WR, DeFor TE, Weisdorf DJ, Davies SM (2003b) High-producer interleukin-2 genotype increases risk for acute graft-versus-host disease after unrelated donor bone marrow transplantation. Transplantation 76(12):1758–1762

Mapara MY, Kim YM, Marx J, Sykes M (2003) Donor lymphocyte infusion-mediated graft-versus-leukemia effects in mixed chimeras established with a nonmyeloablative conditioning regimen: extinction of graft-versus-leukemia effects after conversion to full donor chimerism. Transplantation 76(2):297–305

Mapara MY, Leng C, Kim YM, Bronson R, Lokshin A, Luster A et al (2006) Expression of chemokines in GVHD target organs is influenced by conditioning and genetic factors and amplified by GVHR. Biol Blood Marrow Transplant 12(6):623–634

Markey KA, MacDonald KP, Hill GR (2008) Impact of cytokine gene polymorphisms on graft-vs-host disease. Tissue Antigens 72(6):507–516

Martin PJ (2008) Biology of chronic graft-versus-host disease: implications for a future therapeutic approach. Keio J Med 57(4):177–183

Merad M, Manz MG, Karsunky H, Wagers A, Peters W, Charo I et al (2002) Langerhans cells renew in the skin throughout life under steady-state conditions. Nat Immunol 3(12):1135–1141

Merad M, Hoffmann P, Ranheim E, Slaymaker S, Manz MG, Lira SA et al (2004) Depletion of host Langerhans cells before transplantation of donor alloreactive T cells prevents skin graft-versus-host disease. Nat Med 10(5):510–517

Middleton PG, Taylor PR, Jackson G, Proctor SJ, Dickinson AM (1998) Cytokine gene poly-morphisms associating with severe acute graft-versus-host disease in HLA-identical sibling transplants. Blood 92(10):3943–3948

Miklos S, Mueller G, Chang Y, Schubert TE, Holler E, Hildebrandt GC (2008) Pulmonary function changes in experimental graft-versus-host disease of the lung. Biol Blood Marrow Transplant 14(9):1004–1016

Miklos S, Mueller G, Chang Y, Bouazzaoui A, Spacenko E, Schubert TE et al (2009) Preventive usage of broad spectrum chemokine inhibitor NR58-3.14.3 reduces the severity of pulmonary and hepatic graft-versus-host disease. Int J Hematol 89(3):383–397

Morita NI, Matsumura Y, Morita K, Miyachi Y (2007) Expression of CCR5 in graft-versus-host disease (GVHD) of the skin: immunohistochemical staining of 38 cases. J Dermatol 34(4):254–257

Moser B, Wolf M, Walz A, Loetscher P (2004) Chemokines: multiple levels of leukocyte migration control. Trends Immunol 25(2):75–84

Muller G, Hopken UE, Lipp M (2003) The impact of CCR7 and CXCR5 on lymphoid organ development and systemic immunity. Immunol Rev 195:117–135

Murai M, Yoneyama H, Harada A, Yi Z, Vestergaard C, Guo B et al (1999) Active participation of CCR5(+)CD8(+) T lymphocytes in the pathogenesis of liver injury in graft-versus-host dis-ease. J Clin Invest 104(1):49–57

Murai M, Yoneyama H, Ezaki T, Suematsu M, Terashima Y, Harada A et al (2003) Peyer's patch is the essential site in initiating murine acute and lethal graft-versus-host reaction. Nat Immunol 4(2):154–160

Murphy PM (2002) International Union of Pharmacology. XXX. Update on chemokine receptor nomenclature. Pharmacol Rev 54(2):227–229

Murphy PM, Baggiolini M, Charo IF, Hebert CA, Horuk R, Matsushima K et al (2000) Interna-tional union of pharmacology. XXII. Nomenclature for chemokine receptors. Pharmacol Rev 52(1):145–176

Nash RA, Storb R (1996) Graft-versus-host effect after allogeneic hematopoietic stem cell transplantation: GVHD and GVL. Curr Opin Immunol 8:674–680

New JY, Li B, Koh WP, Ng HK, Tan SY, Yap EH et al (2002) T cell infiltration and chemokine expression: relevance to the disease localization in murine graft-versus-host disease. Bone Marrow Transplant 29(12):979–986

Nishimura M, Kuboi Y, Muramoto K, Kawano T, Imai T (2009) Chemokines as novel therapeutic targets for inflammatory bowel disease. Ann N Y Acad Sci 1173:350–356

Nishio N, Yagasaki H, Takahashi Y, Muramatsu H, Hama A, Tanaka M et al (2009) Late-onset non-infectious pulmonary complications following allogeneic hematopoietic stem cell trans-plantation in children. Bone Marrow Transplant 44(5):303–308

Oettel KR, Wesly OH, Albertini MR, Hank JA, Iliopolis O, Sosman JA et al (1994) Allogeneic T-cell clones able to selectively destroy Philadelphia chromosome-bearing (Ph1+) human leukemia lines can also recognize Ph1- cells from the same patient. Blood 83:3390–3402

Ohl L, Henning G, Krautwald S, Lipp M, Hardtke S, Bernhardt G et al (2003) Cooperating mechanisms of CXCR5 and CCR7 in development and organization of secondary lymphoid organs. J Exp Med 197(9):1199–1204

Okamoto I, Kohno K, Tanimoto T, Iwaki K, Ishihara T, Akamatsu S et al (2000) IL-18 prevents the development of chronic graft-versus-host disease in mice. J Immunol 164(11):6067–6074

Ota A, Yamamoto M, Hori T, Miyai S, Naishiro Y, Sohma H et al (2009) Upregulation of plasma CCL8 in mouse model of graft-vs-host disease. Exp Hematol 37(4):525–531

Palmer LA, Sale GE, Balogun JI, Li D, Jones D, Molldrem JJ et al (2009) Chemokine receptor CCR5 mediates allo-immune responses in Graft-vs-Host Disease. Biol Blood Marrow Trans-plant 16(3):311–319

Panoskaltsis-Mortari A, Taylor PA, Yaegar TM, Wangensteen OD, Bitterman PB, Ingbar DH et al (1997) The critical early proinflammatory events associated with idiopathic pneumonia

syndrome in irradiated murine allogenic recipients are due to donor T cell infusion and potentiated by cyclophoshamide. J Clin Invest 100(5):1015–1027

Panoskaltsis-Mortari A, Strieter RM, Hermanson JR, Fegeding KV, Murphy WJ, Farrell CL et al (2000) Induction of monocyte- and T-cell-attracting chemokines in the lung during the generation of idiopathic pneumonia syndrome following allogeneic murine bone marrow transplantation. Blood 96(3):834–839

Panoskaltsis-Mortari A, Hermanson JR, Haddad IY, Wangensteen OD, Blazar BR (2001) Intercellular adhesion molecule-I (ICAM-I, CD54) deficiency segregates the unique pathophysiological requirements for generating idiopathic pneumonia syndrome (IPS) versus graftversus-host disease following allogeneic murine bone marrow transplantation. Biol Blood Marrow Transplant 7(7):368–377

Panoskaltsis-Mortari A, Hermanson JR, Taras E, Wangensteen OD, Serody JS, Blazar BR (2003) Acceleration of idiopathic pneumonia syndrome (IPS) in the absence of donor MIP-1 alpha (CCL3) after allogeneic BMT in mice. Blood 101(9):3714–3721

Panoskaltsis-Mortari A, Hermanson JR, Taras E, Wangensteen OD, Charo IF, Rollins BJ et al (2004) Post-BMT lung injury occurs independently of the expression of CCL2 or its receptor, CCR2, on host cells. Am J Physiol Lung Cell Mol Physiol 286(2):L284–L292

Panoskaltsis-Mortari A, Tram KV, Price AP, Wendt CH, Blazar BR (2007) A new murine model for bronchiolitis obliterans post-bone marrow transplant. Am J Respir Crit Care Med 176 (7):713–723

Papadakis KA, Prehn J, Moreno ST, Cheng L, Kouroumalis EA, Deem R et al (2001) CCR9-positive lymphocytes and thymus-expressed chemokine distinguish small bowel from colonic Crohn's disease. Gastroenterology 121(2):246–254

Patriarca F, Skert C, Sperotto A, Damiani D, Cerno M, Geromin A et al (2004) Incidence, outcome, and risk factors of late-onset noninfectious pulmonary complications after unrelated donor stem cell transplantation. Bone Marrow Transplant 33(7):751–758

Pavletic SZ, Lee SJ, Socie G, Vogelsang G (2006a) Chronic graft-versus-host disease: implications of the National Institutes of Health consensus development project on criteria for clinical trials. Bone Marrow Transplant 38(10):645–651

Pavletic SZ, Martin P, Lee SJ, Mitchell S, Jacobsohn D, Cowen EW et al (2006b) Measuring therapeutic response in chronic graft-versus-host disease: National Institute of Health Consensus Development Project on criteria for clinical trials in chronic graft-versus-host disease: IV. Response criteria working group report. Biol Blood Marrow Transpl 12:252–266

Pease JE, Horuk R (2009) Chemokine receptor antagonists: part 2. Expert Opin Ther Pat 19 (2):199–221

Pease JE, Williams TJ (2006) The attraction of chemokines as a target for specific anti-inflammatory therapy. Br J Pharmacol 147(Suppl 1):S212–S221

Piper KP, Horlock C, Curnow SJ, Arrazi J, Nicholls S, Mahendra P et al (2007) CXCL10-CXCR3 interactions play an important role in the pathogenesis of acute graft-versus-host disease in the skin following allogeneic stem-cell transplantation. Blood 110(12):3827–3832

Rao AR, Quinones MP, Garavito E, Kalkonde Y, Jimenez F, Gibbons C et al (2003) CC chemokine receptor 2 expression in donor cells serves an essential role in graft-versus-hostdisease. J Immunol 171(9):4875–4885

Reckless J, Tatalick LM, Grainger DJ (2001) The pan-chemokine inhibitor NR58-3.14.3 abolishes tumour necrosis factor-alpha accumulation and leucocyte recruitment induced by lipopolysaccharide in vivo. Immunology 103(2):244–254

Reiss Y, Proudfoot AE, Power CA, Campbell JJ, Butcher EC (2001) CC chemokine receptor (CCR)4 and the CCR10 ligand cutaneous T cell-attracting chemokine (CTACK) in lymphocyte trafficking to inflamed skin. J Exp Med 194(10):1541–1547

Riddell SR, Murata M, Bryant S, Warren EH (2002) Minor histocompatibility antigens–targets of graft-versus-leukemia responses. Int J Hematol 76(Suppl 2):155–161

Rollins BJ (1997) Chemokines. Blood 90(3):909–928

Rot A, Von Andrian UH (2004) Chemokines in Innate and Adaptive Host Defense: Basic Chemokinese Grammar for Immune Cells. Annu Rev Immunol 22:891–928

Sakaida E, Nakaseko C, Harima A, Yokota A, Cho R, Saito Y et al (2003) Late-onset noninfectious pulmonary complications after allogeneic stem cell transplantation are significantly associated with chronic graft-versus-host disease and with the graft-versus-leukemia effect. Blood 102(12):4236–4242

Sakoda Y, Hashimoto D, Asakura S, Takeuchi K, Harada M, Tanimoto M et al (2007) Donor-derived thymic-dependent T cells cause chronic graft-versus-host disease. Blood 109 (4):1756–1764

Saruta M, Yu QT, Avanesyan A, Fleshner PR, Targan SR, Papadakis KA (2007) Phenotype and effector function of CC chemokine receptor 9-expressing lymphocytes in small intestinal Crohn's disease. J Immunol 178(5):3293–3300

Sasaki M, Hasegawa H, Kohno M, Inoue A, Ito MR, Fujita S (2003) Antagonist of secondary lymphoid-tissue chemokine (CCR ligand 21) prevents the development of chronic graft-versus-host disease in mice. J Immunol 170(1):588–596

Sato T, Thorlacius H, Johnston B, Staton TL, Xiang W, Littman DR et al (2005) Role for CXCR6 in recruitment of activated CD8+ lymphocytes to inflamed liver. J Immunol 174(1):277–283

Savani BN, Montero A, Srinivasan R, Singh A, Shenoy A, Mielke S et al (2006) Chronic GVHD and pretransplantation abnormalities in pulmonary function are the main determinants predicting worsening pulmonary function in long-term survivors after stem cell transplantation. Biol Blood Marrow Transplant 12(12):1261–1269

Serody JS, Burkett SE, Panoskaltsis-Mortari A, Ng-Cashin J, McMahon E, Matsushima GK et al (2000) T-lymphocyte production of macrophage inflammatory protein-1alpha is critical to the recruitment of CD8(+) T cells to the liver, lung, and spleen during graft-versus-host disease. Blood 96(9):2973–2980

Shinoda H, Tasaka S, Fujishima S, Yamasawa W, Miyamoto K, Nakano Y et al (2009) Elevated CC chemokine level in bronchoalveolar lavage fluid is predictive of a poor outcome of idiopathic pulmonary fibrosis. Respiration 78(3):285–292

Shlomchik WD, Couzens MS, Tang CB, McNiff J, Robert ME, Liu J et al (1999) Prevention of graft-versus-host disease by inactivation of host antigen-presenting cells. Science 285(5426):412–415

Shulman HM, Sale GE, Lerner KG, Barker EA, Weiden PL, Sullivan K et al (1978) Chronic cutaneous graft-versus-host disease in man. Am J Pathol 91(3):545–570

Slavin S, Naparstek E, Nagler A et al (1993) Graft vs leukemia (GVL) effects with controlled GVHD by cell mediated immunotherapy (CMI) following allogeneic bone marrow transplantation (BMT). Blood 82:423a

Strieter RM, Burdick MD, Gomperts BN, Belperio JA, Keane MP (2005) CXC chemokines in angiogenesis. Cytokine Growth Factor Rev 16(6):593–609

Sugerman PB, Faber SB, Willis LM, Petrovic A, Murphy GF, Pappo J et al (2004) Kinetics of gene expression in murine cutaneous graft-versus-host disease. Am J Pathol 164(6):2189–2202

Sullivan KM, Parkman R (1983) The pathophysiology and treatment of graft-versus-host disease. Clin Haematol 12(3):775–789

Sun Y, Tawara I, Toubai T, Reddy P (2007) Pathophysiology of acute graft-versus-host disease: recent advances. Transl Res 150(4):197–214

Takahashi H, Furukawa T, Hashimoto S, Suzuki N, Kuroha T, Yamazaki F et al (2000) Contribution of TNF-alpha and IL-10 gene polymorphisms to graft-versus-host disease following allo-hematopoietic stem cell transplantation. Bone Marrow Transplant 26(12):1317–1323

Terwey TH, Kim TD, Kochman AA, Hubbard VM, Lu S, Zakrzewski JL et al (2005) CCR2 is required for CD8-induced graft-versus-host disease. Blood 106(9):3322–3330

Teshima T, Ordemann R, Reddy P, Gagin S, Liu C, Cooke KR et al (2002) Acute graft-versus-host disease does not require alloantigen expression on host epithelium. Nat Med 8(6):575–581

Teshima T, Reddy P, Liu C, Williams D, Cooke KR, Ferrara JL (2003) Impaired thymic negative selection causes autoimmune graft-versus-host disease. Blood 102(2):429–435

Tichelli A, Rovo A, Gratwohl A (2008) Late pulmonary, cardiovascular, and renal complications after hematopoietic stem cell transplantation and recommended screening practices. Hematology Am Soc Hematol Educ Program 1:125–133

Truitt RL, Atasoylu AA (1991a) Impact of pretransplant conditioning and donor T cells on chimerism, graft-versus-host disease, graft-versus-leukemia reactivity, and tolerance after bone marrow transplantation. Blood 77:2515–2523

Truitt RL, Atasoylu AA (1991b) Contribution of CD4+ and CD8+ T cells to graft-versus-host disease and graft-versus-leukemia reactivity after transplantation of MHC-compatible bone marrow. Bone Marrow Transplant 8:51–58

Tseng LH, Storer B, Petersdorf E, Lin MT, Chien JW, Grogan BM et al (2009) IL10 and IL10 receptor gene variation and outcomes after unrelated and related hematopoietic cell transplantation. Transplantation 87(5):704–710

Uderzo C, Pillon M, Corti P, Tridello G, Tana F, Zintl F et al (2007) Impact of cumulative anthracycline dose, preparative regimen and chronic graft-versus-host disease on pulmonary and cardiac function in children 5 years after allogeneic hematopoietic stem cell transplantation: a prospective evaluation on behalf of the EBMT Pediatric Diseases and Late Effects Working Parties. Bone Marrow Transplant 39(11):667–675

Ueha S, Murai M, Yoneyama H, Kitabatake M, Imai T, Shimaoka T et al (2007) Intervention of MAdCAM-1 or fractalkine alleviates graft-versus-host reaction associated intestinal injury while preserving graft-versus-tumor effects. J Leukoc Biol 81(1):176–185

Varona R, Cadenas V, Gomez L, Martinez AC, Marquez G (2005) CCR6 regulates CD4+ T-cell-mediated acute graft-versus-host disease responses. Blood 106(1):18–26

Varona R, Cadenas V, Lozano M, Moreno-Ortiz MC, Kremer L, Martinez AC et al (2006) CCR6 regulates the function of alloreactive and regulatory CD4+ T cells during acute graft-versus-host disease. Leuk Lymphoma 47(8):1469–1476

Viola A, Luster AD (2008) Chemokines and their receptors: drug targets in immunity and inflammation. Annu Rev Pharmacol Toxicol 48:171–197

Weiner RS, Mortimer MB, Gale RP, Gluckman E, Kay HEM, Kolb JJ et al (1986) Interstitial pneumonitis after bone marrow transplantation. Ann Intern Med 104:168–175

Weninger W, Crowley MA, Manjunath N, von Andrian UH (2001) Migratory properties of naive, effector, and memory CD8(+) T cells. J Exp Med 194(7):953–966

Wysocki CA, Burkett SB, Panoskaltsis-Mortari A, Kirby SL, Luster AD, McKinnon K et al (2004) Differential roles for CCR5 expression on donor T cells during graft-versus-host disease based on pretransplant conditioning. J Immunol 173(2):845–854

Wysocki CA, Jiang Q, Panoskaltsis-Mortari A, Taylor PA, McKinnon KP, Su L et al (2005a) Critical role for CCR5 in the function of donor CD4 + CD25+ regulatory T cells during acute graft-versus-host disease. Blood 106(9):3300–3307

Wysocki CA, Panoskaltsis-Mortari A, Blazar BR, Serody JS (2005b) Leukocyte migration and graft-versus-host disease. Blood 105(11):4191–4199

Yakoub-Agha I, Saule P, Depil S, Micol JB, Grutzmacher C, Boulanger-Villard F et al (2006) A high proportion of donor CD4+ T cells expressing the lymph node-homing chemokine receptor CCR7 increases incidence and severity of acute graft-versus-host disease in patients undergoing allogeneic stem cell transplantation for hematological malignancy. Leukemia 20(9):1557–1565

Zhang Y, McCormick LL, Desai SR, Wu C, Gilliam AC (2002) Murine sclerodermatous graft-versus-host disease, a model for human scleroderma: cutaneous cytokines, chemokines, and immune cell activation. J Immunol 168(6):3088–3098

Zhou L, Askew D, Wu C, Gilliam AC (2007) Cutaneous gene expression by DNA microarray in murine sclerodermatous graft-versus-host disease, a model for human scleroderma. J Invest Dermatol 127(2):281–292

Zlotnik A, Yoshie O (2000) Chemokines: a new classification system and their role in immunity. Immunity 12(2):121–127