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Reprint of: Emerging Therapeutics for the Control of Chronic Graft-versus-Host Disease ☆

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INTRODUCTION

Chronic graft-versus-host disease (cGVHD) currently represents the leading cause of nonrelapse mortality and morbidity after allogeneic hematopoietic stem cell transplantation (SCT). In parallel with an increased use of granulocyte colony-stimulating factor (G-CSF)-mobilized stem cell products as a graft source, the incidence of cGVHD has dramatically increased. Currently, up to 50% of SCT recipients develop this multisystem inflammatory disease that occurs late after bone marrow transplantation. Although cGVHD can affect almost any target tissue, the predominant and diagnostic organ pathologies that develop are usually cutaneous and/or pulmonary fibrosis (scleroderma and bronchiolitis obliterans, respectively) [1,2]. Unfortunately, as for most diseases with fibrotic manifestations, there is currently no satisfactory therapy for cGVHD. Standard primary treatment is glucocorticoids with or without other immunosuppressive agents; however, nearly 50% of patients continue to have inadequate control of their cGVHD and require second-line systemic treatment [3,4]. Moreover, systemic glucocorticoids are wrought with long term-complications, thereby increasing morbidity and mortality in this patient population that are otherwise cured of their original malignancy.

A much-needed recent surge of preclinical and clinical studies have significantly advanced our understanding of the pathophysiology of cGVHD, which we now recognize as a complex immunologic process incorporating multiple facets of adaptive and innate immunity, including B cells, T cells, and macrophages and their interactions with target tissue. Importantly, these studies have led to the identification of targetable cellular and molecular mediators of cGVHD and have begun to broaden our choice of potential new therapeutics to manage these patients. This review focuses on 3 recently identified therapeutic targets for cGVHD control, IL-17, CSF-1, and Janus kinases (JAKs), and provides an overview of new pharmacologic and cellular approaches currently being implemented in the clinic.

INTERLEUKIN-17A

Both the pathogenesis and histologic features of cGVHD exhibit similarities to autoimmune disease. The proinflammatory cytokine IL-17A (hereafter simply IL-17) has emerged as an important mediator of organ damage associated with autoimmune diseases, including systemic sclerosis, a condition closely resembling scleroderma, the predominant clinical feature of cGVHD after SCT [5,6]. The IL-17 blocking agent secukinumab is approved for treatment in psoriasis, and 2 others, brodalumab (anti-IL-17) and ixekizumab (anti-IL-17 receptor A), are in clinical trials and show promising results [7]. In the setting of cGVHD, studies in preclinical models have demonstrated the development of both skin

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(scleroderma) and lung (bronchiolitis obliterans) pathology to be IL-17 dependent [8,9]. Furthermore, the administration of a neutralizing IL-17 mAb during established disease in a lung cGVHD model effectively reversed cGVHD features [10]. These data, together with reported elevated circulating IL-17 levels in patients late after SCT at a time point when cGVHD develops [11], highlight IL-17 blockade as a promising therapeutic strategy for cGVHD.

T EFFECTOR CELL–DERIVED IL-17: TH17/TC17

Donor T cells contained within the stem cell graft are critical mediators of cGVHD pathology. The inflammatory milieu induced by conditioning promotes host dendritic cell priming of donor alloreactive T cells and polarization toward IL-17 secreting CD4 (Th17) and CD8 (Tc17) T cell lineages. Th17/Tc17 differentiation has been demonstrated to be highly dependent on IL-6, which is found at elevated levels early after SCT [11,12], and to a lesser extent transforming growth factor (TGF)-β and IL-12/IL-23p40 [13,14]. Additionally, stem cell mobilization with G-CSF was demonstrated to promote IL-17 production from both CD4 and CD8 T cells [9]. After SCT, Th17/Tc17 rapidly sequester in GVHD target organs (skin, lung, liver) where they promote pathology [13,14], thus providing a link between cGVHD predilection and granulocyte peripheral blood stem cell grafts.

Cytokine profiling of Th17/Tc17 after SCT in preclinical models demonstrated co-expression high levels of multiple proinflammatory cytokines including IFN-γ, tumor necrosis factor, IL-13, CSF-1, and granulocyte-macrophage CSF and highlighting their polyfunctional nature [13,14]. However, Tc17 expression of cytolytic effector molecules such as granzyme B and the degranulation marker CD107a (Lamp1) is limited, and although demonstrated mediators of GVHD, Tc17 are unable to mediate the graft-versus-leukemia effect, making them an attractive therapeutic target [13]. Notably, IL-17 expression by Th17/Tc17 is only transient in spite of maintained expression of the lineage defining transcription factor RAR-related orphan receptor γt (ROR-γt) [13,14]. Thus, targeting ROR-γt to attenuate Th17/Tc17 differentiation may provide clinical benefit. In support of this, pharmacologic inhibition of ROR-γt reduces TH17 cells and limits pathology in mouse models of autoimmunity and intestinal inflammation and cGVHD [10,15,16]. Importantly, in line with elevated levels of IL-17, circulating Th17 are increased in SCT patients, and high-level expression of CD146 marks these cells during active disease in both mice and man [10,14]. CD146 expression on T cells identifies subsets with transendothelial migration capacity and has a suggested mechanistic role in Th17 polarization [17]. Indeed, grafts containing CD146 KO T cells, compared with wild-type T cells, elicited fewer Th17, and cGVHD in these recipients was significantly attenuated [10]. Although the mechanism by which tissue-infiltrating Th17/Tc17 promote the fibrotic manifestations of cGVHD is incompletely understood, evidence points to a role in promoting fibrogenic macrophage differentiation and accumulation in cGVHD target organs. In this regard IL-17 was shown to control the sequestration of macrophages within the skin and lung [9,10], and reduced Th17 and improved pulmonary function in recipients of grafts containing CD146 KO T cells was associated with a marked decrease in pulmonary macrophages [10].

CSF-1, MONOCYTES, AND MACROPHAGES

CSF-1 controls macrophage development, differentiation, and survival [18]. Although CSF-1 is a critical cytokine for macrophage homeostasis in steady state, populations elicited by CSF-1 are associated with, and exacerbate, a broad spectrum of pathologies [18] including fibrosis [19,20]. In mice, circulating monocytes can be fractionated into $CCR2^{+}Ly6C^{hi}$ (hereafter $CCR2^{+}$) and $CCR2^{neg}Ly6C^{lo}$ (hereafter $Ly6C^{lo}$) subsets. $CCR2^{+}$ monocytes are a proinflammatory subset, whereas $Ly6C^{lo}$ monocytes are patrolling resident macrophage precursors. CSF-1 promotes $CCR2^{+}$ monocyte differentiation into $Ly6C^{lo}$ monocytes and the conversion of $Ly6C^{lo}$ monocytes into tissue resident macrophages, which in turn exhibit long-term CSF-1 dependency [18,21]. Within cGVHD lesions, macrophages are abundant and are found in close proximity to collagen-producing myofibroblasts [22]. Activated macrophages can contribute to fibrosis via their production of profibrotic mediators (eg, TGF-β, MCP-1, IL-13, and platelet-derived growth factor), which directly promote myofibrobast differentiation and function [23-26]. After SCT skin-infiltrating macrophages express the receptor for CSF-1 and CD206 but not iNOS, identifying them as alternatively activated (M2-like) macrophages. Importantly, CSF-1 administration after experimental SCT expands blood $Ly6C^{lo}$ monocytes and enhances macrophage infiltration into the skin, resulting in significantly increased skin pathology [8]. Moreover, CSF-1 receptor blockade after SCT diminishes $Ly6C^{lo}$ monocytes and tissue macrophages, resulting in markedly reduced cutaneous and pulmonary fibrosis and improved pulmonary function. In this setting fibrotic pathology was dependent on TGF-β expression by infiltrating myeloid cells, including $Ly6C^{lo}$ monocytes [8,27].

The mechanism by which IL-17 promotes tissue sequestration of profibrogenic macrophages remains unclear. However, monocytes and macrophages can express IL-17RA and IL-17RC, the receptor subunits required for IL-17 signal transduction [28], suggesting that direct IL-17 signaling in these cells may contribute to pathogenic CSF-1–dependent monocyte/macrophage differentiation after transplant. Indeed, direct IL-17 signaling has been implicated in $CCR2^{+}$ to $Ly6C^{lo}$ monocyte conversion [29] macrophage polarization [30] and functions as a potent chemoattractant (equivalent to CCL2) for the murine J447 macrophage cell line [31]. IL-17 regulates many inflammatory target genes through synergistic signaling with other cytokines, including tumor necrosis factor [32]. Like CSF-1 receptor blockade, IL-17RA deficiency has been shown to reduce the number of circulating $Ly6C^{lo}$ monocytes, and IL-17 treatment induced proinflammatory mediators (IL-6, CCL2, IL-1α) in CSF-1 differentiated macrophages and primed responses to inflammatory stimuli [29]. These findings demonstrate $Ly6C^{lo}$ monocyte-derived M2 macrophages as mechanistic mediators of fibrosis and highlight the broad clinical potential of targeting monocytes/macrophages and CSF-1 as antifibrotic strategies.

IMPORTANCE OF JAK INHIBITOR SELECTIVITY IN IMMUNITY

The JAK family of nonreceptor tyrosine kinases, which includes JAK1, JAK2, JAK3, and Tyk2, regulates signal transduction of a wide range of cytokines, many of which modulate GVHD and T cell function [33]. Indeed, targeting cytokine signal transduction via JAK inhibition is reported to significantly reduce GVHD in mice [34-36] and humans [36,37]. Several JAK inhibitors that exert unique selectivity against the various JAK molecules are clinically available. The selectively by the JAK inhibitors has direct implications on human immune responses and should be well understood when designing GVHD clinical trials.