Angiogenic factors and inflammation in steroid-refractory acute graft-vs-host disease

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Steroid-refractory acute graft-vs-host disease (aGVHD) remains a frequent and often fatal complication of allogeneic hematopoietic cell transplantation. Recent evidence suggests that angiogenic factors—growth factors that contribute to blood vessel development—may be involved in tissue healing and restitution after inflammatory insults such as aGVHD. However, some angiogenic factors may also be involved in inflammation and worsen clinical outcomes. In this review, we summarize the data relevant to angiogenic factors that may contribute to healing after aGVHD (epidermal growth factor and vascular endothelial growth factor A) and angiogenic factors that may promote inflammation after aGVHD (placental growth factor and follistatin). It is currently unknown whether changes in these factors are a cause or a consequence of aGVHD. Mechanistic studies in the coming years will clarify their roles and identify new pathways for improving outcomes in steroid-refractory aGVHD. (Translational Research 2016;167:80–87)

Abbreviations: aGVHD = acute GraftVSHost Disease; CR = Complete response; EGF = Epidermal growth factor; EGFR = The EGF receptor; FS = Follistatin; GI = Gastrointestinal; HCT = Hematopoietic Cell transplantation; IL = Interleukin; ILC2 = Innante Lymphoid type 2 cells; ILCs = Innate Lymphoid cells; IV = Intravenous; PLGF = Placental growth factor; TNF-a = Tumor necrosis factor alpha; Treg = Regulatory T Cells; VEGF-A = Vascular endothelial growth fact A

INTRODUCTION

Steroid-refractory acute graft-vs-host disease (aGVHD) is a life-threatening complication of allogeneic hematopoietic cell transplantation (HCT) affecting 11% of transplant recipients.[1] In this condition, an immunocompromised host's organs are attacked by immunocompetent lymphocytes from the donor graft without clinical improvement after the accepted first-line therapy, corticosteroids. As a result of the immunologic attack, target organs and tissues can be badly damaged, leading to inflammatory cytokine release (eg, tumor necrosis factor alpha [TNF-α]) into the circulation, which can fuel ongoing immune activation in a vicious cycle.[2]

Damage to the gastrointestinal (GI) tract is the major cause of morbidity and mortality in most patients with steroid-refractory aGVHD (although severe skin aGVHD presenting with erythroderma, bulla formation, and desquamation and severe liver aGVHD presenting with marked cholestasis can also be observed). Patients with steroid-refractory aGVHD of the GI tract typically have severe diarrhea (often >2 L daily), with abdominal pain and cramping, intermittent ileus, and at times, overt GI bleeding. They endure prolonged hospital stays measured in weeks to months, are often unable to eat, receive intravenous (IV) nutrition support, develop anasarca related to hypoalbuminemia, are at risk for bacteremia because of compromised gut barrier function, and are often debilitated by steroid myopathy

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and malnutrition. Endoscopically, the intestinal tract of patients with severe GI aGVHD often demonstrates mucosal erythema, loss of vascular markings, and ulceration.[3] Histologically, crypt loss, epithelial and endothelial cell apoptosis, and precapillary hemorrhage are observed in these patients.[4,5] Intensification of immunosuppression, the standard approach to steroid-refractory aGVHD at present, results in neither complete correction of malabsorption nor long-term survival in most patients.[6,7] In addition, intensification of immunosuppression can have a profoundly negative effect on infectious immunity, significantly increasing risk of life-threatening infections. New approaches that can promote restoration of epithelial and endothelial integrity and promote normal mucosal immune homeostasis without impairing the immune response to infections are urgently needed. Aside from mucoadherent platelet lysates[8] and intralesional injection of mesenchymal stromal cells into oral surfaces damaged by steroid-refractory chronic GVHD (NCT02055625), the concept of mucosal healing as an end point has not been extensively studied in allogeneic HCT recipients.

Both endothelial cell damage and neovascularization play a role in the pathophysiology of aGVHD. In the 1970s, the concept of "lymphocyte-induced angiogenesis" was introduced, where adoptive transfer of thymus-derived lymphocytes was observed to cause a quantifiable increase in vascular reticulation in immunocompromised recipients.[9] Although it was clear from historical studies that mature lymphocytes were the main effectors in the lymphocyte-induced angiogenesis reaction, the soluble mediators involved in host vascular proliferation were unknown. In the years that followed, several factors critical for angiogenic responses were discovered, with the first prototypic angiogenic factor, vascular endothelial growth factor A (VEGF-A, initially known as vascular permeability factor), discovered in the 1980s.[10,11] In general, angiogenic factors are characterized by their participation in blood vessel development, wound healing, and tissue regeneration after injury. More recently, vascular endothelial trophic factors have also been described for modulating immune responses,[12,13] which could have significant implications for the pathophysiology and treatment of steroid-refractory aGVHD.

Approximately 5 decades after the first description of a host vascular proliferative response accompanying aGVHD,[14] Luft et al provided critical evidence that endothelial damage, not recalcitrant T-cell activity, characterizes refractory aGVHD,[15] where patients with refractory aGVHD had increasing levels of serum thrombomodulin and increased angiopoietin 2/VEGF ratios, indicating endothelial vulnerability in refractory patients. In a multivariate analysis of nonrelapse mortality, increased angiopoietin 2/VEGF ratio >10 was associated with a 17.5-fold increased risk of death.[15] The phenomenon of endothelial cell damage and subsequent vascular response possibly arises in a manner similar to the classic description of the pathogenesis of aGVHD itself, with endothelial damage as a result of the conditioning regimen, followed by T-cell activation against host endothelial cells, followed by apparent neovascularization in an effort to repair damaged tissues. Interestingly, epithelial injury—the clinical hallmark of aGVHD—might be considered a secondary event after initial endothelial cell damage caused by alloreactive T cells.[16,17] The dichotomy of endothelial cell damage and neovascularization in aGVHD remains an area of active investigation.

Recently, studies involving patient samples from multicenter aGVHD treatment trials have expanded the number of angiogenic factors of interest in the pathophysiology of steroid-refractory aGVHD. Alterations in VEGF-A and 3 other circulating angiogenic factors—epidermal growth factor (EGF), placental growth factor (PlGF), and follistatin (FS)—were associated with important clinical outcomes, including response to therapy and survival in a pilot study and 2 validation cohorts.[18] In samples collected from patients with aGVHD compared with controls (1) plasma levels of EGF were markedly lower in patients with aGVHD, in particular those without a complete response (CR) to first-line therapy with corticosteroids, and EGF levels decreased after 28 days in patients with no response to corticosteroids; (2) plasma VEGF-A was low at the onset of aGVHD, but increased after 28 days in patients with CR to first-line corticosteroids; (3) plasma and serum PlGF and FS were increased at the onset of aGVHD compared with controls; and (4) increased FS predicted poor 6-month survival after aGVHD. These findings, as summarized in Table I, suggest that some angiogenic factors may attenuate, whereas others may exacerbate, inflammation in aGVHD.

With neovascularization and endothelial damage both involved in the pathophysiology of aGVHD,[15,19] interest in studying angiogenic factors for their potential healing and inflammatory roles in aGVHD has grown. Angiogenic factors in general are classified as such by their ability to contribute to the growth of new blood vessels, although the balance of some angiogenic factors may also determine clinical outcomes—repair and regeneration vs ongoing damage and inflammation—in aGVHD. In this review, we will discuss recent findings in the context of what is currently known regarding the role of EGF, VEGF-A, PlGF, and FS in tissue repair and inflammation in models that are relevant to aGVHD. It is possible