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Placental Growth Factor: What Hematologists Need to Know

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Abstract

Although first identified in placenta, the angiogenic factor known as placental growth factor (PlGF) can be widely expressed in ischemic or damaged tissues. Recent studies have indicated that PlGF is a relevant factor in the pathobiology of blood diseases including hemoglobinopathies and hematologic malignancies. Therapies for such blood diseases may one day be based upon these and ongoing investigations into the role of PlGF in sickle cell disease, acute and chronic leukemias, and complications related to hematopoietic cell transplantation. In this review, we summarize recent studies regarding the potential role of PlGF in blood disorders and suggest avenues for future research.

Keywords

placental growth factor; sickle cell anemia; leukemia; hematopoietic cell transplantation; graft-versus-host disease

Introduction

Increasing evidence has established a link between the complex processes of inflammation and angiogenesis, both characterized and exacerbated by the production of numerous cytokines, chemokines, growth factors, and prostaglandins by cell types such as endothelial cells and macrophages[1-4]. Just as uncontrolled inflammation can lead to ongoing tissue damage, unrestrained or aberrant production of angiogenic factors can contribute to tumor pathogenesis and the inflammatory response[5,6]. In this review, we discuss the emerging data demonstrating a role for one such angiogenic factor, placental growth factor (PlGF), in hematologic diseases – both as a potential biomarker and as a possible driver of disease

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pathogenesis – in the setting of benign and malignant hematology, as well as in hematopoietic cell transplantation (HCT).

In 1991, a novel angiogenic factor was isolated and cloned from a human placental cDNA library, and thus named placental growth factor[7]. PlGF is a member of the vascular endothelial growth factor (VEGF) family, which also includes the structurally and functionally related angiogenic factors VEGF-A, VEGF-B, VEGF-C, VEGF-D, and VEGF-E[8]. Despite sharing only 42% amino acid sequence identity, the three-dimensional structures of PlGF and VEGF-A show significant similarity[9]. However despite this structural similarity, whereas VEGF-A can bind to both the VEGF receptor 1 (VEGFR-1, also called fms-like tyrosine kinase-1 or FLT1) and VEGF receptor 2 (VEGFR-2, also named fetal liver kinase Flk1/KDR), PlGF-1 can only bind to VEGFR-1 and the soluble form of VEGFR-1 (sFlt-1) which is lacking the transmembrane and intracellular domains[10]. The binding of VEGF-A or PlGF-1 to sFlt-1 is thought to serve as an anti-angiogenic regulatory mechanism, as both ligands can bind with high affinity but are unable to signal because of the missing tyrosine kinase domain[11].

The human *PGF* gene is mapped to chromosome 14q24[12], and in humans four isoforms have been identified, PlGF-1-4, due to alternative mRNA splicing[7,12-15]. These isoforms differ in size, heparin-binding affinity, VEGF receptor binding, and tissue expression patterns; a detailed review of biological characteristics and receptor binding affinities of PlGF isoforms was published by Ribatti[16]. In this review, we will focus on the PlGF-1 isoform, the most commonly studied isoform in humans, hereafter referred to as PlGF. While PlGF expression is highest and best characterized in the placenta and decidual tissues[17], low level PlGF expression has also been detected in endothelial cells[18] and bone marrow erythroblasts[19]. Additionally, pathologic upregulation of PlGF has been described in diverse tissue types including thyroid, heart, lung, skeletal muscle, and adipose tissue[15,18,20-22].

Both PlGF and VEGF-A can activate receptor-mediated signal transduction as homodimers, or as PlGF/VEGF heterodimers; the PlGF/VEGF heterodimers demonstrate overlapping but biologically different effects, suggesting that PlGF may modulate VEGF effects via heterodimer formation and serve as a means of angiogenic, mitogenic, and chemotactic control[23]. PlGF was initially thought to influence downstream signal transduction indirectly, displacing VEGF-A from both membrane and soluble forms of VEGFR-1, and thus leading to enhanced VEGF-A binding to VEGFR-2[24], the receptor responsible for mediating the majority of VEGF-A downstream effects[25]. However, accumulating evidence suggests a broader mechanism for PlGF signaling[26]: PlGF can regulate inter- and intramolecular crosstalk between VEGFR-1 and VEGFR-2, amplifying VEGF-A mediated signaling through the VEGFR-2; in addition, VEGF/PlGF heterodimers can activate VEGFR-1/VEGFR-2 receptor heterodimers with an enhanced angiogenic response[27]. Compared to VEGFR-2, comparatively less is known about pathways downstream of and functions mediated by VEGFR-1[28]. However, studies in endothelial cells, fibroblasts, and monocytes have demonstrated that PlGF-mediated VEGFR-1 activation can influence the phosphatidylinositol-3 (PI3) kinase, protein kinase B (Akt), mitogen-activated protein kinase (MAPK) kinase-1/2 (MEK-1/2), and extracellular signal-regulated kinase-1/2 (ERK-1/2)

pathways, as well as the Janus kinase-signal transducer and activator of transcription 3 (JAK/STAT3) pathway [29-35].

Perhaps best defined as a placental-derived regulatory factor in pregnancy, PlGF in this setting is thought to contribute to an angiogenic switch, and a pathogenic role for (low) PlGF levels and the subsequent development of preeclampsia has been described[36]. During normal third trimester pregnancy levels of PlGF increase, with a peak at week 30, followed by a subsequent decline in PlGF and increase in sFlt-1 levels until delivery[37]. In the setting of preeclampsia however, these changes are intensified and occur at earlier time points: increased serum sFlt-1 levels can be detected approximately 5-weeks before the onset of preeclampsia, while serum PlGF levels are significantly lower in women later developing preeclampsia as early as 13-16 weeks of gestation, compared to controls[36]. Additionally, increases in the sFlt-1 to PlGF ratio have been found to correlate with the development of preeclampsia [38].

While some studies have suggested that PlGF is redundant for normal vascular development with knockout mice lacking an aberrant phenotype, these knockout mice demonstrate impaired angiogenesis during pathologic conditions such as ischemia[26]. PlGF is known to stimulate the growth, migration, and survival of endothelial cells[27,39], and is also a chemoattractant for macrophages[40,41] and bone marrow progenitor cells[42,43]. Unlike VEGF expression, PlGF levels are low or undetectable in healthy tissue, but increased in the setting of diseases[44,45]. Potential involvement for PlGF has been described in wound healing, collateral vessel formation in ischemia, and tumor growth[46,47], and a role for PlGF homodimers, PlGF/VEGF heterodimers, and their receptors in rheumatoid inflammation via the triggering of proinflammatory cytokine production has been reported[48,49].

Indeed, emerging evidence suggests that the biologic effect of PlGF may be in pathological angiogenesis and inflammation. Given its mitogenic and migratory effects on endothelial cells and macrophage chemoattractant properties, as well as the link between aberrant angiogenesis and inflammation, PlGF is clearly no longer a pregnancy-specific factor. Instead, PlGF appears to be a key regulatory factor involved in controlling angiogenic and inflammatory responses via its VEGF-competitive binding to the VEGF receptors and sFlt-1, through PlGF/VEGF homodimer/heterodimer formation, and through activation of downstream signaling pathways controlling cytokine and chemokine production. We review the evidence for PlGF as a marker and driver of hematologic disease in the following sections.

PlGF in benign hematologic diseases

Recent observations have described a potential role for PlGF in the pathogenesis of benign hematologic diseases, and particularly in sickle cell disease (SCD). Given the high morbidity from vaso-occlusive events in SCD, there have been considerable studies on the vascular endothelium in SCD and its interaction with red blood cells. Factors contributing to increased red cell adhesion include platelet activation and subsequent release of thrombospondin, leading to a bridge between endothelial cells and sickle red cells, as well as inflammatory cytokine-mediated upregulation of vascular-cell adhesion molecule 1

(VCAM-1) on endothelial cells, which can interact with the integrin complex expressed on sickle red cells[50]. Additionally, endothelial dysfunction in SCD has been demonstrated by impairment of shear stress-mediated vasodilation[51] and by aberrant flow mediated arterial dilatation[52]. Increased intra- and extravascular hemolysis occurring in SCD also leads to the release of free hemoglobin, heme, and reactive oxygen and nitrogen species, which can modulate levels of the vasodilator nitric oxide[53], as well as contribute to the activation of reds cells, leukocytes, platelets, and endothelial cells [54,55]. In patients with SCD, compared to healthy controls, increased serum levels of adhesion molecules (sCD40 ligand, E-selection, intracellular adhesion molecule 1 [ICAM-1], and VCAM-1)[52], angiogenic factors (angiopoietin-1 [Ang-1], erythropoietin [EPO], soluble tunica intima endothelial kinase 2 [sTIE2], and PlGF)[56], and inflammatory cytokines (tumor necrosis factor-alpha [TNF], interleukin-8 [IL-8], IL-17)[57,58] have been described. Elevation of such factors may provide evidence of a possible link between inflammation and angiogenesis in SCD pathogenesis, and in SCD complications including acute and chronic lung disease (airway hyperresponsiveness, pulmonary hypertension) and iron overload resulting from chronic hemolytic anemia and chronic red cell transfusions, and has led to studies on the role of inflammatory angiogenic factors (such as PlGF) in SCD.

Given the known state of leukocyte and endothelial cell activation in SCD, as well as elevated levels of VEGF and enhanced erythropoiesis, Perelman et al hypothesized in a 2003 *Blood* report[59] that PlGF levels may be high in SCD, and that PlGF levels may also correlate with leukocyte activation and vaso-occlusive events. They determined that PlGF expression, produced by erythroid cells, was increased in bone marrow light density mononuclear cells (LD-MNCs) from patients with SCD compared to normal donor LD-MNCs[59]. Serum PlGF levels were higher in patients with severe SCD, defined as at least 3 vaso-occlusive crises per year, compared to those with mild disease and normal controls. The authors also found that PlGF significantly increased mRNA levels of pro-inflammatory cytokines and chemokines in normal donor peripheral blood mononuclear cells, that these same cytokines and chemokines were elevated in the plasma of sickle cell patients, and that PlGF stimulated monocyte chemotaxis[59]. Mechanistically, Selvaraj et al described that in SCD, monocyte activation by PlGF was mediated through VEGFR-1, leading to increased transcription of inflammatory cytokines and chemokines by normal donor monocytes and by the monocytic cell line THP-1. Inhibition of PI3 kinase/AKT and its downstream targets MEK-12 and ERK-1/2 attenuated PlGF-mediated cytokine and chemokine mRNA expression[35].

PlGF has also been shown to induce expression of both the vasoconstrictor endothelin-1 from human microvascular endothelial cells, and the endothelin-B receptor in monocytes, possibly contributing to inflammation and pulmonary hypertension in sickle cell disease[60]. Using a lentivirus vector, Sundaram et al induced PlGF expression in normal mice, matching the elevated levels of PlGF seen in sickle mice, and as a consequence found increased endothelin-1 levels as well as increased right ventricular pressures and right ventricular hypertrophy. These results correlated with clinical features in SCD patients, including elevated endothelin-1 and tricuspid regurgitant velocity, an echocardiographic marker of risk for high pulmonary artery pressure[61].

An increased incidence of airway hyperresponsiveness has also been described in children and adults with SCD[62-64], and emerging evidence suggests a possible contributing role for PlGF in leukotriene-mediated inflammation[65]. Leukotrienes are known mediators of bronchoconstriction, with a critical role in triggering acute asthma as well as in mediating airway hypersensitivity in chronic asthma[66]. Elevated levels of leukotrienes have also been described in SCD patients at steady state, with further increased levels associated with vaso-occlusive events and acute chest syndrome[67] as well as with increased hospitalizations for pain[68]. Patel et al demonstrated that peripheral blood mononuclear cells (MNCs) from SCD patients showed significantly increased mRNA expression of molecules involved in the leukotriene pathway (5-lipoxygenase and 5-lipoxygenase activating protein [FLAP]), that PlGF induced leukotriene production in MNCs and a monocytic cell line, and that PlGF-mediated increase in FLAP mRNA involved activation of PI3 kinase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and hypoxia inducible factor-1 alpha[69]. In a PlGF-deficient mouse model, PlGF deficiency reduced allergen-induced airway hyperresponsiveness as well as activation of the leukotriene pathway. Treatment of sickle mice with an anti-PlGF antibody blocked airway hyperreactivity to allergens, as did treatment with a 5-lipoxygenase inhibitor[69]. These results suggest a role for PlGF in the pathogenesis of SCD airway hyperresponsiveness through the induction of inflammatory mediators such as leukotrienes.

The association between PlGF and its soluble receptor (sFlt-1) has been investigated, given the potential regulatory role of sFlt-1 as a 'ligand-binding sink.' Perhaps best studied in the setting of preeclampsia, a pregnancy complication characterized by endothelial dysfunction and dysregulation of circulating angiogenic factors[36], sFlt-1 levels have also been studied in SCD. In contrast to the inverse relationship seen between PlGF and sFlt-1 in preeclampsia, sFlt-1 levels have been found to be elevated at baseline in sickle cell patients, although without further increase during acute pain crises[70]. Circulating levels of sFlt-1 were also elevated in the setting of SCD pulmonary hypertension, and correlated significantly with markers of hemolysis including lactate dehydrogenase (LDH), total and indirect bilirubin, and reticulocyte count, suggesting a potential role of sFlt-1 in inducing endothelial dysfunction in this setting[71].

An association between PlGF and β-thalassemia has also been explored. Perelman et al found increased PlGF levels in bone marrow LD-MNCs from patients with β-thalassemia compared to normal donor LD-MNCs[59]. Circulating levels of PlGF were also significantly elevated in patients with compound heterozygous sickle cell disease and β-thalassemia, and again correlated positively with markers of hemolysis (LDH, reticulocyte counts, uric acid). Ferritin levels also correlated positively with PlGF, suggesting a possible role for iron overload in the biology of SCD [72].

The regulation of PlGF expression in patients with hemoglobinopathies is not completely understood. Erythropoietin has been shown to increase PlGF transcript levels in normal bone marrow $CD34^+$ erythroid cells[59]. Given the association between PlGF and marker levels for iron overload (ferritin, transferrin), Wang et al hypothesized that iron overload could also regulate the expression of PlGF. They identified that heme-bound iron (hemin) induced PlGF mRNA expression in the human erythroblastoid cell line K562, in a time- and dose-

dependent manner. Additionally, expression of PlGF first required expression of the iron-induced gene erythroid Kruppel-like factor (EKLF); EKLF then bound directly to the PlGF promoter[73]. Thus, as proposed by Wand et al, these results suggest a model in which increased erythropoiesis and ongoing red cell hemolysis leads to erythroid hyperplasia and increased erythropoietin levels, which subsequently induce the expression of PlGF in erythroid cells. Increased PlGF is also stimulated by iron overload, occurring as a result of recurrent red cell transfusions, suggesting multiple pathways may lead to the marked increase in PlGF observed in patients with hemoglobinopathies.

An observational study regarding the role of PlGF in sickle acute chest syndrome, conducted through the Children's Hospital Medical Center in Cincinnati in collaboration with the National Heart, Lung, and Blood Institute (NCT00448370), is estimated to be completed this year. Additionally, a study sponsored by Nemours Children's Clinic investigating the molecular phenotyping of asthma in SCD, including plasma PlGF levels as a secondary outcome, has completed enrollment (NCT01879592). Whether PlGF will ultimately best serve as a biomarker of disease risk in patients with hemoglobinopathies, or as a central driver of disease pathogenesis via leukocyte activation and endothelial cell dysfunction, as well as the potential role of targeted therapies directed at modulating its effects, remain active areas of ongoing investigation.

PlGF in hematologic malignancies

In contrast to the focus on abnormal blood vessel development within tumors in solid tumor oncology, angiogenesis in the setting of hematologic malignancies involves the complex interplay between the diverse cells of the bone marrow microenvironment including tumor cells, endothelial cells and stem cell progenitors, as well as the surrounding bone marrow stromal cells. While the association of angiogenic factors in malignant hematologic diseases has perhaps been best described for VEGF and its receptors (VEGFR-1, VEGFR-2)[74-79], there is emerging evidence to suggest that PlGF specifically may also contribute to the pathogenesis of hematologic malignancies, such as chronic myeloid leukemia (CML) as well as acute myeloid and acute lymphoid leukemias (AML, ALL). Fragoso et al noted that activation of the VEGFR-1 receptor modulates the distribution of ALL cells within and egress out of the bone marrow along VEGF and PlGF gradients, with PlGF enhancing the proliferation and migration of ALL cells in vitro. VEGFR-1 neutralization increased leukemia cell apoptosis and reduced peripheral circulation of the leukemic cells[80]. The authors also noted that CML and AML samples (both primary cells and cell lines) highly expressed VEGFR-1[80]. In a follow-up report, Casalou et al determined that PlGF induced AML cell migration more potently than control (and more potently than VEGF treatment), with increased formation of VEGFR-1 membrane protrusions which were also seen in AML primary cells. PlGF enhanced the phosphorylation of ERK-1/2 and p38, as well as the activation of Rho-GTPases. AML cell lines treated with PlGF also showed increased activation of the actin-binding protein cofilin and formation of lipid rafts, and leukemia cell migration and proliferation were inhibited by an actin-depolymerizing agent[81]. These results suggest that PlGF may enhance AML cell proliferation and migration, potentially at least in part via modulation of the actin cytoskeleton.

To further determine the role of PlGF in ALL biology and cell survival, Ikai et al quantified PlGF expression in bone marrow cells from patients with B-ALL using real time RT-PCR. Interestingly, they found a significant increase in PlGF expression levels in samples from patients with Philadelphia chromosome (Ph) positive ALL compared to Ph- ALL samples (this difference was not found for VEGF expression)[82]. In cell cultures of Ph+ and Ph- ALL cell lines, PlGF also selectively enhanced the growth of the Ph+ cell line in a time- and dose-dependent manner, an effect that was abrogated by the addition of VEGFR1/Fc (which binds to and blocks the function of PlGF). These results suggest a potential role for PlGF in Ph+ ALL disease, via autocrine and paracrine PlGF-VEGFR1 signaling[82].

Given these suggestive links between PlGF and leukemia, Schmidt et al explored the role of PlGF in CML using a mouse model of imatinib-resistant BCR-ABL1^{+} disease[83]. PlGF mRNA transcript levels in the bone marrow, and peripheral blood PlGF plasma levels, were increased in CML mice, compared to healthy or mock-transduced mice. Additionally, cultured CD45^{-} bone marrow stromal cells (BMSCs) from CML mice also contained more PlGF transcripts than did BMSCs from healthy mice. In co-culture systems of murine BMSCs with human leukemic cells, using enzyme-linked immunosorbent assays (ELISA) for murine versus human PlGF detection, murine PlGF secretion in co-cultures was increased above levels found in monocultures, and induced in an NF-kβ-dependent manner, indicating that the human CML cells stimulated murine PlGF production by BMSCs. In addition, PlGF also influenced the proliferation of BCR-ABL1^{+} cells, with a PlGF dose-dependent increase in 3H-Thymidine incorporation and in numbers of CML cells; these proliferative effects were blocked by an anti-PlGF antibody. In murine models comparing wild type mice transplanted with wild type bone marrow cells transduced with BCR-ABL1, versus transplanted BCR-ABL1^{+} PlGF$^{-/-}$ marrow cells into PlGF$^{-/-}$ mice, CML onset occurred later in the knockout-knockout mice than in wild type-wild type mice, and the knockout-knockout mice survived longer. An anti-PlGF monoclonal antibody delayed leukemia progression and prolonged survival of CML mice, compared to an isotype-matched IgG control, and this survival benefit was seen in both imatinib-treated and imatinib-resistant mice. Importantly, the authors also determined that PlGF levels were significantly elevated in the plasma of patients at time of diagnosis of chronic phase CML, compared to healthy donors; plasma PlGF levels were also significantly higher in samples from patients in blast crisis compared to the chronic phase samples, providing *in vivo* evidence of a possible link between PlGF and CML pathogenesis[83]. These results support the notion that PlGF may be contributing to the pathogenesis of malignant hematologic diseases, and the role of anti-angiogenic and targeted anti-PlGF therapy in this setting merits further investigation in such pre-clinical models.

Anti-angiogenic therapy has been developed as a treatment option for solid tumor malignancies, with first generation agents being monoclonal antibodies targeting VEGF, and subsequently second generation therapies were developed including receptor tyrosine kinase inhibitors of the VEGF receptors. Clinical trial results of anti-angiogenic agents have identified concern for possible acquired escape from VEGF blockade[84,85], uncovering the need for additional strategies such as targeting the normalization of tumor vasculature or other angiogenic factors. These strategies include PlGF manipulation as a means to target the myeloid cell compartment and affect the polarization of tumor-associated macrophages

[86], as well as to prevent anti-angiogenic escape[44]. A neutralizing murine anti-PlGF monoclonal antibody has been developed and tested in preclinical murine cancer models and human xenograft models[87]. Anti-PlGF therapy inhibited the growth and metastasis of multiple tumor models, inhibited intratumoral macrophage infiltration, and amplified the effect of cytotoxic chemotherapy; importantly, anti-PlGF treatment did not induce an anti-angiogenic escape program (in contrast to anti-VEGFR2 therapy) and demonstrated a superior safety profile compared to VEGF(R)-inhibitors[44]. Recently, the results of a phase I, dose escalation study of a humanized anti-PLGF monoclonal antibody (TB-403, ThromboGenics/BioInvent) in patients with advanced solid tumors was reported[88]. Among the 23 patients with metastatic or unresectable solid tumor malignancies receiving treatment with TB-403, the most frequently occurring adverse events were fatigue, constipation, pyrexia, dyspnea, nausea, and cough; one patient developed a lung embolus deemed possibly related to TB-403. There were 3 patient deaths related to disease progression and not considered drug-related. While the study was not designed to determine efficacy, 6 patients receiving TB-403 had stable disease at week-8, and 2 patients demonstrated disease stability for 12-months. Thus, preclinical studies, as well as emerging evidence from the solid tumor setting, suggest that therapeutic targeting of PlGF in the setting of hematologic malignancies may also potentially hold therapeutic promise, by influencing not only angiogenic factor levels and VEGF receptor(s) activation, but also through the modulation of monocyte activation and migration.

PlGF in allogeneic hematopoietic cell transplantation

Hematopoietic cell transplantation is a potentially curative therapeutic modality for life-threatening benign hematologic diseases as well as high-risk or refractory hematologic malignancies. HCT requires engraftment of healthy donor cells into a patient's bone marrow compartment to restore hematopoiesis and immune function. PlGF may play both physiologic and pathologic roles in allogeneic HCT. Recent studies suggest that PlGF may be involved in hematopoietic stem cell (HSC) mobilization and maintenance of the HSC vascular niche[42,89,90]. Outside of the marrow compartment, PlGF may be involved in repair of certain tissues damaged by the transplant conditioning regimen (e.g., intestinal mucosa[91]), but yet may also contribute to inflammation in graft-versus-host disease (GVHD)[92]. In this section, the role of PlGF in the context of HCT and its possible contribution to HCT outcomes and complications will be reviewed.

HCT requires mobilization, homing, and proliferation of otherwise quiescent donor HSC and progenitor cells to/from the recipient bone marrow compartment. Some of these critical processes may be enhanced by PlGF. Hattori et al. demonstrated that PlGF restores hematopoiesis following bone marrow suppression by at least two mechanisms. First, PlGF overexpression in mice using an adenoviral vector was shown to enhance chemotaxis of VEGFR-1+ hematopoietic stem and progenitor cells, leading to a 20-fold increase of these cells in the circulation[42]. HSCs mobilized by PlGF were capable of engrafting into lethally irradiated mice, suggesting that PlGF may be a potential therapeutic adjunct to assist in clinical HSC mobilization, currently assisted by cytokines such as granulocyte colony stimulating factor (G-CSF) or therapeutics that block HSC/stromal interactions, such as plerixafor[93]. In subsequent studies involving both mice and non-human primates, PlGF

showed synergism in mobilization of HSCs, without added toxicities, when combined with G-CSF [89]. A second mechanism by which PlGF may enhance hematopoiesis is by exerting a protective role for HSCs within the marrow microenvironment. In their pivotal 2002 study, Hattori et al. also showed that PlGF provides critical growth factor signals for cell differentiation and acceleration of the later phase of hematopoietic recovery through upregulation of matrix metalloproteinase-9 (MMP9), causing release of soluble Kit ligand, an important stem cell growth factor[42]. The most significant source of PlGF in the marrow appears to be the central marrow endothelial cells, protecting primitive HSCs within their vascular niche to a greater degree than marrow stromal cells[90]. Related research suggests that PlGF also attenuates inflammatory cytokine-suppressed erythropoiesis[94] and enhances platelet production via megakaryocyte maturation[95], both of which may be of utility in the many patients with anemia and thrombocytopenia post-HCT. More studies are needed to validate these findings in transplant models and in clinical studies, as well as to elucidate the potential benefit of PlGF in normal hematopoiesis versus its role in inflammatory angiogenesis.

Although it may seem beneficial to hematopoiesis based upon these prior studies, recent data also suggests that PlGF may also reflect or contribute to post-HCT inflammation. A pre-clinical model has demonstrated that low-dose irradiation, akin to what may be given as a component of pre-HCT conditioning, increases plasma PlGF[96]. An elevation in plasma PlGF after conditioning has recently been observed in the clinical setting, where patients undergoing allogeneic HCT had over 10-fold higher plasma PlGF levels compared to healthy donors[97]. Furthermore, patients with acute GVHD enrolled on two multicenter acute GVHD treatment trials had significantly higher levels of circulating PlGF than a control cohort of allogeneic HCT recipients without acute GVHD[97]. Other factors, including conditioning regimen intensity, severity of acute GVHD or specific organ involvement with acute GVHD, showed no significant association. These results have recently been validated in a separate cohort of allogeneic HCT recipients enrolled on a randomized multicenter study of acute GVHD prophylaxis regimens[98]. PlGF levels were significantly elevated both at day 0 (pre-transplant) and at day 100 after HCT among patients who developed acute GVHD, compared to those patients not developing acute GVHD. Additionally, PlGF levels were significantly higher in HCT recipients with treatment-refractory acute GVHD (e.g. steroid-refractory acute GVHD), compared to both HCT recipients with treatment-responsive acute GVHD and those without any acute GVHD. These results suggest that PlGF may not only serve as a marker of inflammatory post-HCT complications such as acute GVHD, but additionally given the day 0 correlation, these findings suggest that PlGF may also contribute to the pathogenesis and subsequent development of acute GVHD.

The cellular source of circulating PlGF in allogeneic HCT or acute GVHD is not known. It is expressed intensely in skin involved with acute GVHD, although in gastrointestinal GVHD, PlGF expression appears diminished compared to healthy controls[92]. This expression pattern is similar to what has been observed in human autoimmune diseases, with increased cutaneous PlGF expression in psoriatic lesions[99], and decreased intestinal PlGF expression in active inflammatory bowel disease[100]. These early observations emphasize the need for additional studies of PlGF in the pathogenesis of acute GVHD, noting that the

effects of PlGF on chronic GVHD, post-transplant relapse, or other late effects, such as cardiovascular disease[101-103], are also not yet known.

Future considerations

Given the known role of inflammation as a driver in the pathogenesis of benign and malignant hematologic diseases[104], as well as increasing evidence establishing a link between inflammation and angiogenesis, further investigation of the role of angiogenic factors and PlGF in these settings is merited. Whether PlGF is simply a biomarker of disease activity and/or severity, or more directly involved in the pathobiology, remains to be determined. While exogenous PlGF supplementation is being considered as a therapeutic adjunct for preeclampsia, anti-angiogenic or anti-PlGF blockade may provide a novel treatment strategy for benign and malignant hematologic diseases, including post-HCT complications such as GVHD. Clarification of the role of PlGF in normal angiogenesis and hematology, versus its involvement in aberrant angiogenesis and inflammation, will be instructive in terms of guiding therapeutic options and in predicting potential side effects.

Research Agenda

- Evaluate PlGF as a biomarker and driver of disease severity in hemoglobinopathies and other benign hematologic diseases.
- Determine the role of PlGF in the pathogenesis and disease progression of hematologic malignancies.
- Develop models to discern the hematopoietic support versus inflammatory role of PlGF in HCT.

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