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REVIEW

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.

1. 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 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

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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.

2. 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].