Majalah Kedokteran Sriwijaya
Th.55 Nomor.1 January 2023

THE ROLE OF PLACENTAL GROWTH FACTOR AS A PARAMETER IN PREECLAMPSIA A REVIEW OF ITS BIOMOLECULAR CHARACTERISTICS

Yuri Kamila[1], Irfanuddin[2]

[1]Biomedical Science Doctoral Programme Faculty of Medicine, Universitas Sriwijaya, Palembang
[2]Department of Physiology, Faculty of Medicine, Universitas Sriwijaya, Palembang

yurikamila151@gmail.com

Abstrak

Preeklampsia adalah hipertensi pada kehamilan yang berhubungan dengan 2% sampai 8% komplikasi kehamilan di seluruh dunia. Preeklampsia didiagnosis bila tekanan darah ≥ 140/90 mmHg setelah usia kehamilan 20 minggu pada dua kali pemeriksaan dengan selang waktu minimal 4 jam atau ≥ 160/100 mmHg dalam interval pendek. Beberapa biomarker telah diidentifikasi. Salah satunya adalah *placental growth factor* (PlGF) yang merupakan bagian dari faktor pertumbuhan endotel vaskular. Biomarker ini terlibat dalam aktivasi sel yang berasal dari sumsum tulang, stimulasi endotel, dan angiogenesis patologis. Beberapa jalur pensinyalan terlibat dalam preeklampsia, seperti jalur pensinyalan JAK-STAT. Penelitian ini bertujuan untuk meninjau karakteristik biomolekular PlGF sebagai parameter pada preeklampsia.

Kata kunci: preeklampsia, faktor pertumbuhan plasenta, bioinformatika

Abstract

The role of placental growth factor as a parameter in preeclampsia: a review of its biomolecular characteristics. Preeclampsia is hypertensive disorder in pregnancy related to 2% to 8% of pregnancy-related complications worldwide. Preeclampsia is diagnosed when blood pressure ≥ 140/90 mmHg after 20 weeks of gestation on two occasions at least 4 hours apart or ≥ 160/100 mmHg in a short interval. Several biomarkers have been identified. One of them is placental growth factor (PlGF) which is a member of the vascular endothelial growth factor family. It is involved in bone marrow- derived cell activation, endothelial stimulation, and pathological angiogenesis. Several signaling pathways involve in preeclampsia, such as JAK-STAT signaling pathway. This study aims to review the biomolecular characteristics of PlGF as a parameter in preeclampsia.

Keywords: *preeclampsia, placental growth factor, bioinformatics*

1. INTRODUCTION

Preeclampsia a common and serious hypertensive disorder in pregnancy, responsible for one-tenth of maternal mortality in Africa, Asia; up to 25% of maternal mortality in Latin America is associated hypertension in pregnancy. Preeclampsia is mainly diagnosed in clinical sense: blood pressure above 140/90 mmHg in the second half of pregnancy and proteinuria (more than 300 mg/24 h urine protein).[1,2]

Some potential markers of preeclampsia are hCG, INHA, PAPPA, PGF, and sFlt-1, with PGF showing most consistent predictor across different studies.[3,4] Placental Growth Factor (PGF) is a part of VEGF-like family coded in 14q24.3, spanning 13.7 kilobases long.[5–7] PGF acts as growth factor and involved in positive regulation of cellular proliferation.[5,7] PGF acts as growth factor controlling trophoblast growth and differentiation during invasion to decidua.[6] In preeclampsia and IUFGR, significantly lower serum PGF level is observed.[1,8] Therefore, we aim to bring shine the light to PGF, based on bioinformatics, the biomolecular characteristics of PGF gene and its physiological role.

2. METHOD

FASTA of PGF gene and PGF protein was obtained from NCBI GenBank (gene ID: 5228; NC_00014.9; NP_003864.2). Physiochemical properties of PGF were conducted on ProtParam and ProtScale. Protease activity prediction was performed on PeptideCutter. Prediction of transmembrane helices of PGF was conducted in TMHMM-2.0. The location of target protein was conducted on TargetP. The pathway analysis of PGF was conducted on KEGG Pathway.

3. RESULTS

Although the official name of gene encoding placental growth factor is PGF, PGF has few aliases: PGFL; PIGF; PLGF; PIGF-2; D12S1900; and SHGC-10760. The PGF is identified in GeneID by its number: 5228.

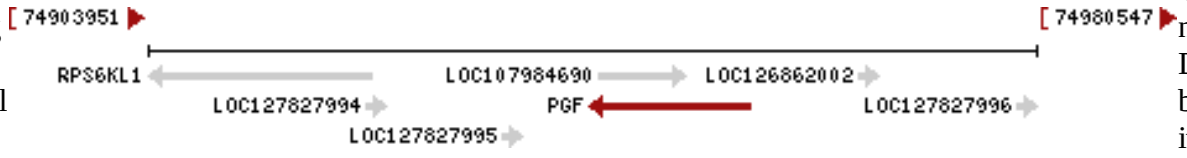


Figure 1. location of PGF gene

Current (at the time of writing) accession version of PGF numbered NC_000014.9. PGF is located in chromosome 14q24.3 in human.[5]

Highest expression of PGF is in placenta, as can be expected, then followed by thyroid gland and prostate as distant third. Study of PGF expression was performed with 95 individuals tissue samples (representing 27 different tissues) (BioProject no. PRJEB4337; April 2018). Placental expression of PGF is highest, with mean of 36.087 ± 24.433 RPKM in 4 samples.

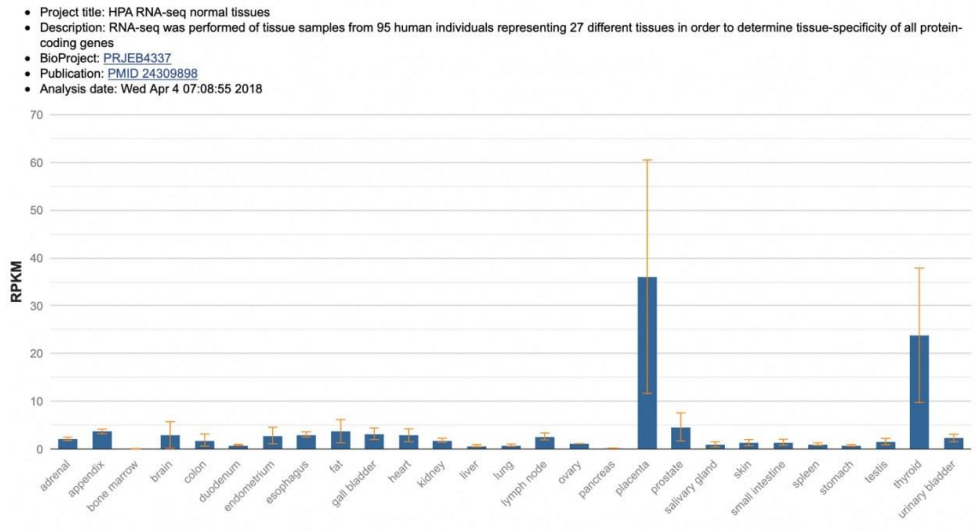


Figure 2. Expression of *PGF* Across Different Organs

Thyroid expressed PGF at 23.087 ± 14.075 RPKM in 4 samples, while prostate expressed PGF at 4.641 ± 2.926 RPKM in 4 samples. Other tissues expressing PGF is adrenal, appendix, brain, colon, duodenum, endometrium, esophagus, fat, gallbladder,

heart, kidney, liver, lung, lymph node, ovary, salivary gland, skin, small intestine, spleen, stomach, testis, and urinary bladder.[5]

```
mpvmrlfpcf lqllaglalp avppqwalsa gngssevevv pfqevwgrsy cralerlvdv
vseypseveh mfspscvsll rctgccgden lhcvpvetan vtmqllkirs gdrpsyvelt
fsqhvrcecr plrekmkper rrpkgrgkrr rekqrptdch lcgdavprr
```

Figure 3. FASTA sequence of PGF protein (NP_002623.2)

The PGF expressed into PGF protein. Current accession version of PGF at the time of writing is NP_002623.2 and the sequence can be found above. From the available sequence information, the next step of analysis can be conducted. First, we determined the theoretical physical and chemical properties of PGF. In this regard, ProtParam was used. Input of FASTA sequence of PGF yielded results shown below.

Figure 4. Composition of PGF

Number of amino acids: 169

Molecular weight: 19210.34

Theoretical pI: 8.96

Amino acid composition: CSV format

Ala (A)	8	4.7%
Arg (R)	20	11.8%
Asn (N)	3	1.8%
Asp (D)	5	3.0%
Cys (C)	11	6.5%
Gln (Q)	6	3.6%
Glu (E)	14	8.3%
Gly (G)	10	5.9%
His (H)	4	2.4%
Ile (I)	1	0.6%
Leu (L)	17	10.1%
Lys (K)	6	3.6%
Met (M)	5	3.0%
Phe (F)	5	3.0%
Pro (P)	15	8.9%
Ser (S)	12	7.1%
Thr (T)	5	3.0%
Trp (W)	2	1.2%
Tyr (Y)	3	1.8%
Val (V)	17	10.1%
Pyl (O)	0	0.0%
Sec (U)	0	0.0%
(B)	0	0.0%
(Z)	0	0.0%
(X)	0	0.0%

Total number of negatively charged residues (Asp + Glu): 19
Total number of positively charged residues (Arg + Lys): 26

Atomic composition:

Carbon	C	832
Hydrogen	H	1344
Nitrogen	N	254
Oxygen	O	237
Sulfur	S	16

Formula: $C_{832}H_{1344}N_{254}O_{237}S_{16}$
Total number of atoms: 2683

Extinction coefficients:

Extinction coefficients are in units of M^{-1} cm^{-1}, at 280 nm measured in water.

Ext. coefficient	16095
Abs 0.1% (=1 g/l)	0.838, assuming all pairs of Cys residues form cystines

Ext. coefficient	15470
Abs 0.1% (=1 g/l)	0.805, assuming all Cys residues are reduced

Estimated half-life:

The N-terminal of the sequence considered is M (Met).

The estimated half-life is: 30 hours (mammalian reticulocytes, in vitro).
>20 hours (yeast, in vivo).
>10 hours (Escherichia coli, in vivo).

Instability index:

The instability index (II) is computed to be 74.81
This classifies the protein as unstable.

Aliphatic index: 75.44

Grand average of hydropathicity (GRAVY): -0.385

Figure 5. Expected Chemical Properties of PGF

ProtParam analysis showed PGF was formed by 169 amino acids, with estimated weight of 19.2 kDa. The estimated isoelectric point (pI) of PGF is 8.96, resulting from combination of both negatively charged residues (aspartic acid and glutamine: 19) and positively charged residues (arginine and lysine: 26). The main constituting amino acids of PGF is arginine (11.8%), followed by leucine and valine at equal terms (10.1%).

Molecular formula of PGF is expected to be C832H1344N254O237S16 with estimated half-life of PGF is around 30 hours in mammalian reticulocytes. The predicted extinction coefficient at 280 nm in water is 16,095 M-1cm-1 (15479 M-1cm-1 when all cysteine residues are reduced). The predicted instability index is 74.81 (thus, classified as unstable protein).

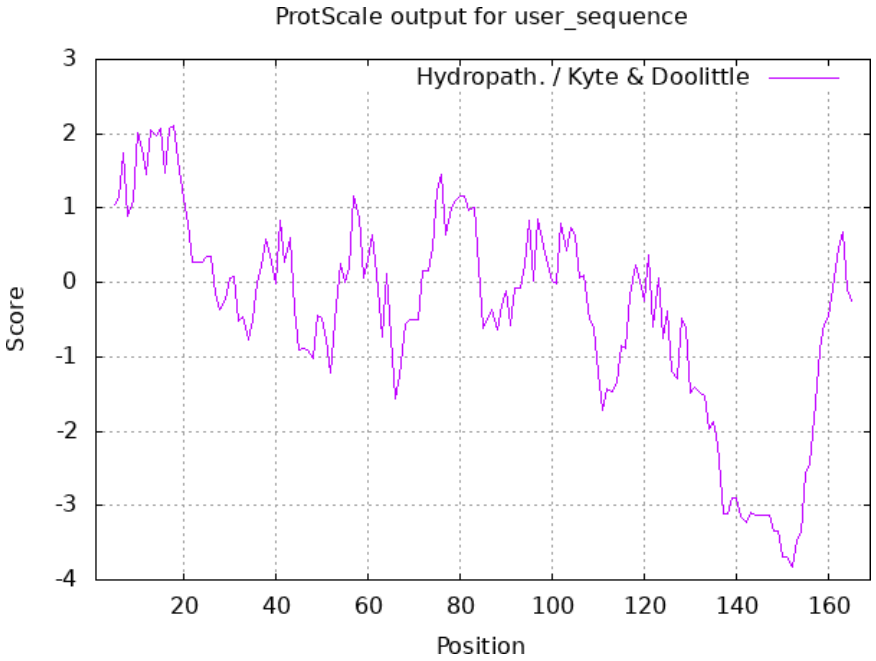
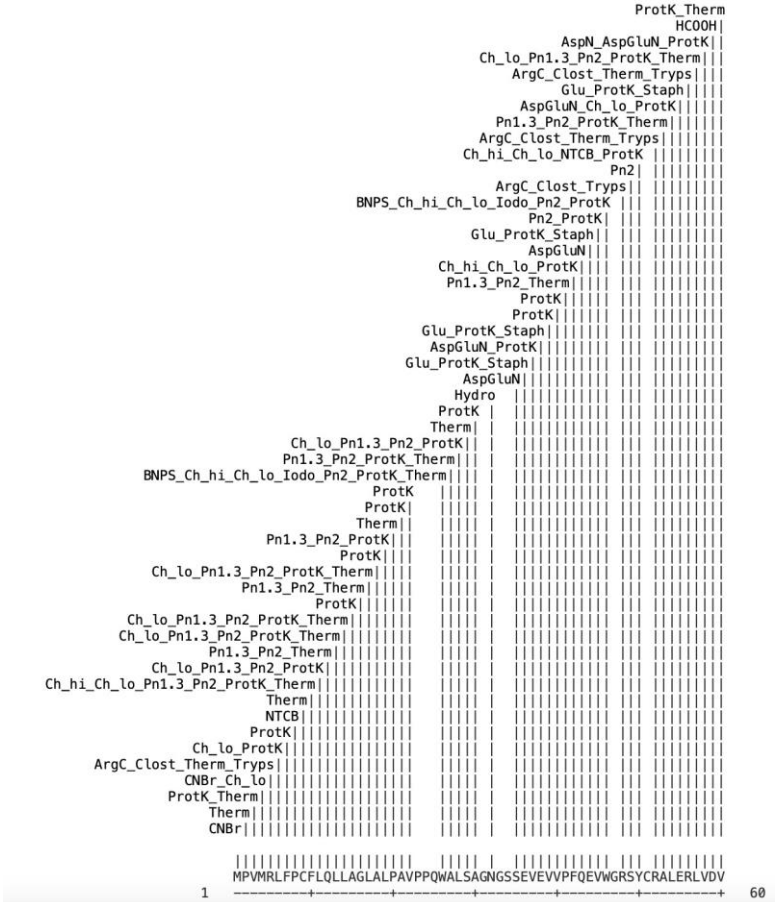


Figure 6. Hydrophobicity Analysis of PGF with ProtScale

The hydrophobicity analysis was conducted using ProtScale. The simulated data showed hydropathy ranged from -3.822 to 2.111 and shown with Kyte-Doolittle Plot.

Similar method was utilized with ProtParam: FASTA sequence was pasted into the input area.



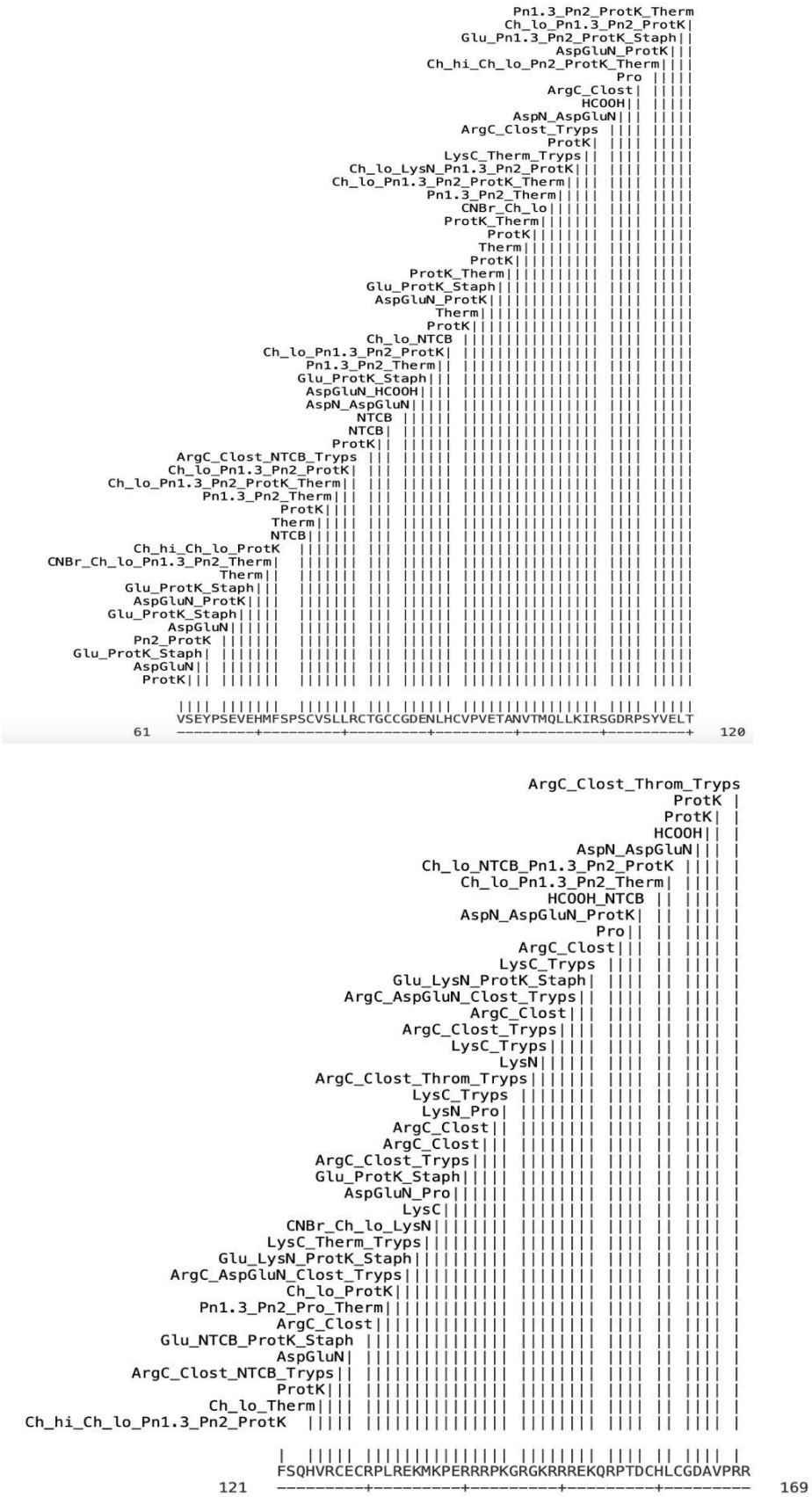


Figure 7. Peptide Cutter Prediction of Proteinases Activity

Analysis of predicted protease activity was conducted on PeptideCutter. Highest predicted possible number of cleavages come from proteinase K (72 cleavages), followed by thermolysin (39 cleavages), low- specificity chymotrypsin (31 cleavages). Other possible proteinases include Arg-C proteinase, Asp-N endopeptidase, Asp-N endopeptidase with N-terminal glutamine, high-specificity chymotrypsin, clostripain, glutamyl endopeptidase, pepsin (at pH 1.3), staphylococcal peptidase I, and trypsin.

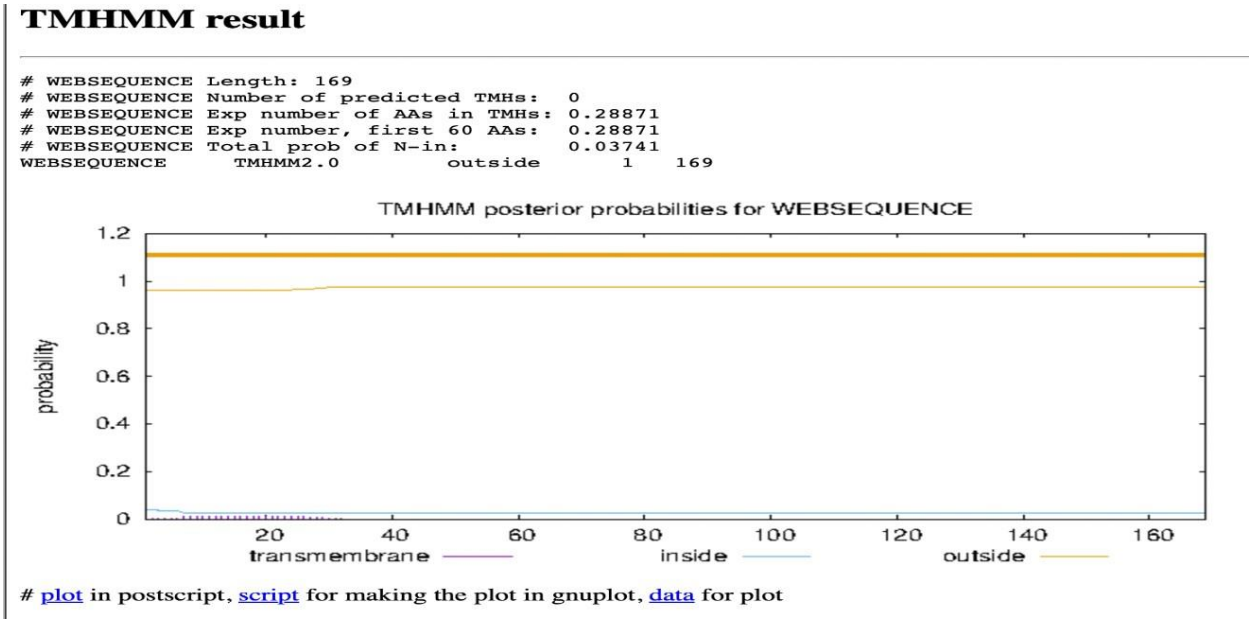


Figure 8. predicted Transmembrane Helices of PGF

Afterwards, we conducted prediction of PGF transmembrane location using TMHMM-2.0. Our result predicted zero transmembrane helix (TMH) of PGF. Our result also predicted that < 1 amino acid is located in transmembrane helices, with < 1 of first 60 amino acids are located in transmembrane region. Total probability of N-terminus of PGF to be located in transmembrane region is very slight (0.03741). Overall, TMHMM-2.0 predicted that all 169 amino acids of PGF are located outside of cells, in accordance with our knowledge that PGF is known soluble growth factor5,7. To further confirm our suspicion, we conducted analysis of PGF role with TargetP-2.0.

Protein type	Other	Signal peptide	Mitochondrial transfer peptide
Likelihood	0.0042	0.9951	0.0008

Figure 9. Predicted Role of PGF

The probable function of PGF was analyzed with TargetP-2.0. From available protein sequence data, the PGF protein very highly likely serves as signal peptide (0.9951). This is in accordance with our knowledge, where PGF serves as soluble growth factor.[5,7]

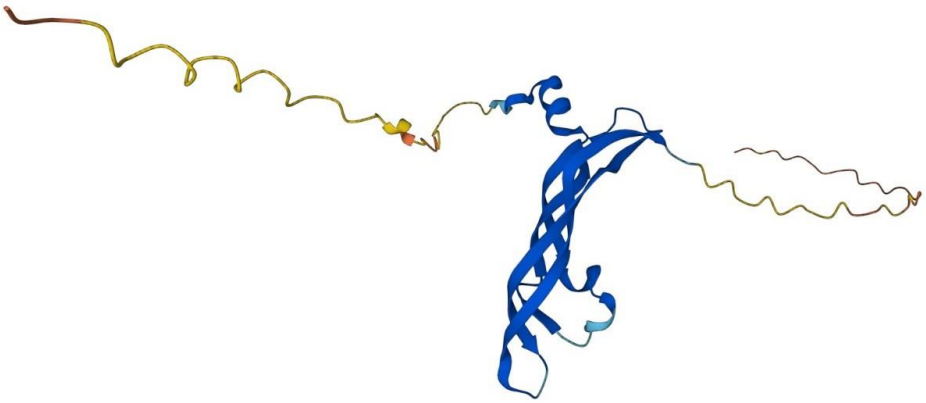


Figure 10. AlphaFold Predicted Structure of PGF

Structural simulation of PGF protein was shown above. The data was taken from AlphaFold database. The PGF consists of 169 amino acids and structured in similar way with VEGF, acting on same receptors.

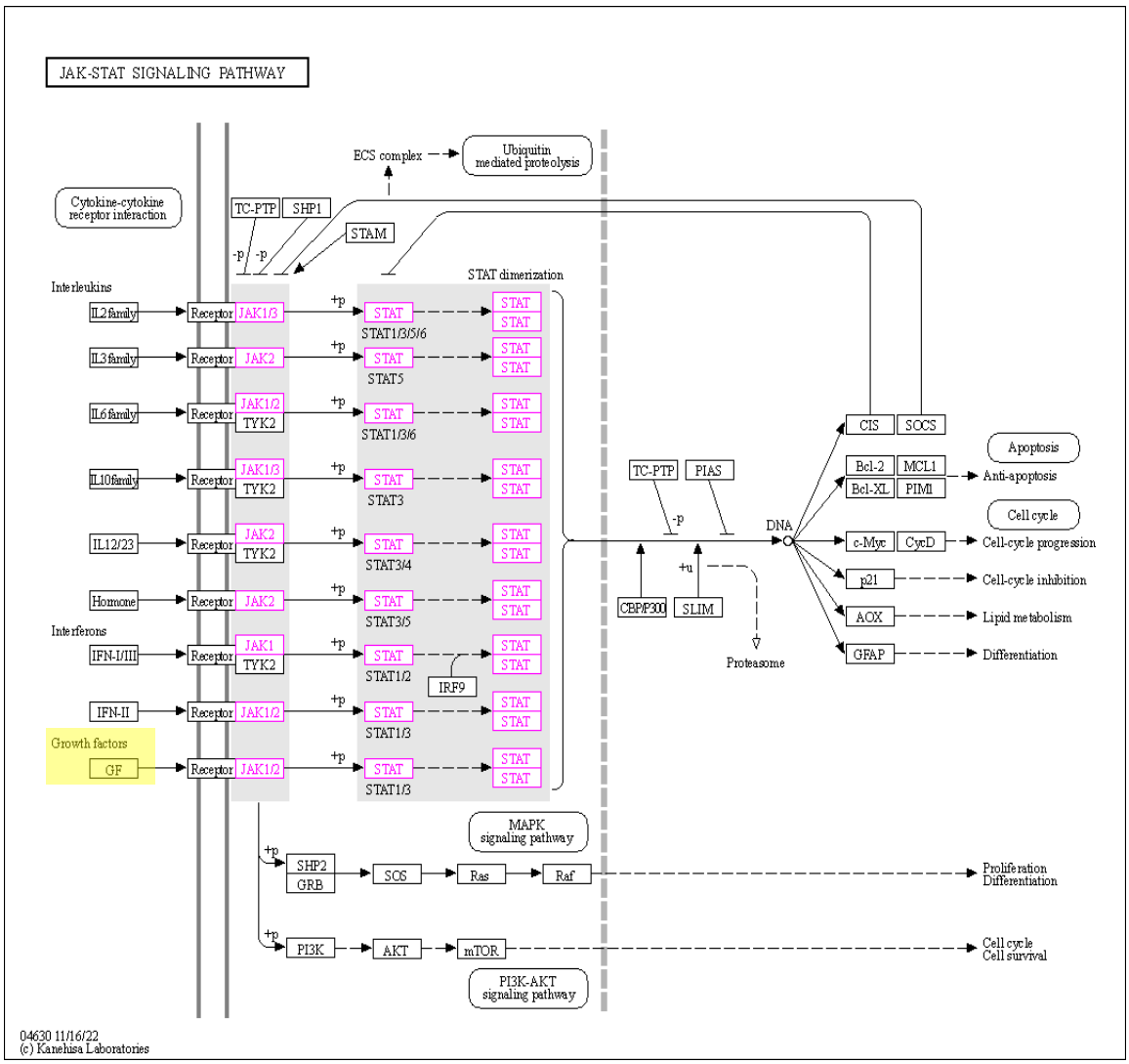


Figure 11. JAK/STAT Pathway

The PGF is a known growth factor in placental development. It is known that PGF acts in JAK/STAT pathway[6] and has been pictured above (originally from KEGG Pathway). Highlighted yellow part shows growth factors, including PGF, acts on its receptors, invoking JAK pathway through STAT into DNA and acts on cell cycle. The STAT pathway can also involve MAPK and PI3K-AKT to regulate proliferation, differentiation, and survival of the cell.[9]

4. DISCUSSION

Preeclampsia is common, serious hypertensive disorder in pregnancy affecting approximately 5%. Around 10% of maternal mortalities in Africa and Asia came from preeclampsia. Meanwhile, around a quarter of maternal mortalities in Latin America is associated with hypertension during pregnancy. Preeclampsia is associated with increased blood pressure (in excess of 140/90 mmHg) in later half of pregnancy and proteinuria in excess of 300 mg/24 h. Preeclampsia is considered as one of the three leading causes of maternal and fetal mortality and/or related complications.[1] Screening criteria of preeclampsia diagnosis are: systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg from two measurements at least 4 hours apart, or shorter interval of systolic blood pressure > 160 mmHg or diastolic blood pressure > 110 mmHg. the increased blood pressure must be first identified after 20 weeks of gestation to qualify as preeclampsia.[10]

Although preeclampsia is commonly sporadic (and sporadically common), genetic factors are thought to play a role in disease susceptibility. More than 70 candidate preeclampsia-related genes have been studied.[6,7] In addition, biomarkers, such as hCG, INHA, PAPPA, PGF, and sFlt-1 have been widely investigated as predictors for adverse outcomes.[3,4,11] In one example, measurement of maternal serum PGF and PAPP-A, in combination with known maternal risk factors (i.e., maternal age, obesity, hypertension, family health history, etc.) and uterine artery measures by Doppler ultrasound, is able to detect 95% of early- onset preeclampsia (< 34 weeks) with a 5% false detection rate in a Caucasian population. Despite the promising result, these risk factors can vary by population. Among different studies, maternal serum PGF level has been shown to be the most consistent predictor for preeclampsia.[3]

PGF is a member of VEGF family, containing 75.13 kb6,7. The human PGF is located in chromosome 14q24.3; the analogue gene of the mouse is located on chromosome 12qD. Both genes are formed by seven exons spanning 13.7 kb in human and 10.4 kb in mouse exclusive of the upstream and downstream regulatory sequences. The name itself, placental growth factor, refers to placenta since the gene was first cloned from a human placental cDNA library.[6] The PGF codes PGF; a protein located in extracellular region and active in extracellular space. PGF in circulation enables its action as a growth factor and is involved in positive regulation of cell proliferation.[5,7]

Alternative splicing of the PGF yields three different isoforms of the mature human PGF protein. The two predominant forms, PGF-1 and PlGF-2 (also known as PlGF-131 and PlGF-152, respectively), differ only by the insertion of a highly basic 21-amino acid stretch at the carboxyl end of the protein. This additional basic region allows PGF-2 to bind heparin1. Alternative splicing of PGF encodes four isoforms: PGF 1-4, composed by 131, 152, 203, and 224 amino acids after the removal of signal peptide (18 amino acids residues in length), respectively. The primary difference between the four isoforms is that PGF-1 and PGF-3 are non-heparin binding diffusible isoforms, while PGF-2 and PGF-4 have additional (highly basic 21 amino acids) heparin binding domains. The PGF-1 dimer consists of two α-helices and seven β-strands per monomer, which are covalently linked by two inter-chain disulphide bonds in an anti-parallel fashion. Structural and mutagenesis

analyses indicated that two negatively-charged residues located in the β3-β4 loop (Asp72 and Glu73) are critical for receptor binding. Other residues crucial for receptor recognition are located in the N-terminal α-helix as well as on the β6 strand. The mutation of one (Asn84) of the two glycosylated residues of PGF reduced binding activity, indicating that, unlike VEGF-A12, glycosylation plays an important role in receptor binding function of PGFs.[6]

PGF is highly expressed in placenta throughout all stages of gestation. It has been proposed to control trophoblast growth and differentiation, thus suggesting a role for the protein during invasion of the trophoblast into the maternal decidua. Immunohistochemistry analyses revealed the presence of PGF in the vasculosyncytial membrane and in the large blood vessels of the placenta. In-situ hybridization analysis also reveals the presence of PGF in the villous trophoblast. Meanwhile, VEGF-A is expressed in cells of mesenchymal origin within the chorionic plate outside placenta cells.[6,12]

PGF expression is also controlled at a post-transcriptional level with a mechanism already described for other growth factors and for many oncogenes. The 5' untranslated region of PGF mRNA contains a small open reading frame, potentially coding for a short peptide (13/15 amino acids in human and five amino acids in mouse), whose deletion or mutation of potential initiator codons, substantially increase PGF expression.[6]

PGF is proposed to regulate vascular development and trophoblast growth and differentiation. Unlike VEGF, which is required for angiogenesis and endothelial cell maintenance, PGF is redundant for vascular development and selectively binds Flt-1/sFlt- 1 (soluble FMS-like tyrosin kinase-I). in this regard, sFlt-1 acts as binding protein, reducing free PGF able to impart its action on VEGFR receptors.[2,13,14] PGF is necessary for stimulating endothelial cell growth, migration, and survival and plays a primary role in pathologic angiogenesis, including in cancer and tissue ischemia. In normal pregnancy, serum PGF level significantly increases. In placenta, PGF is expressed in giant trophoblast cells and decidua natural killer cells.[1] Lower PGF level in pregnancy significantly predicts the risk of preeclampsia and IUFGR, suggesting reduced expression of PGF might be significant in pathological placenta-related conditions.[8,14,15]

In addition to regulation of cellular proliferation and trophoblast invasion, PGF also regulates vasodilation of uterine, myometrial, mesenteric, and subcutaneous arteries.[15] In pregnancy, this effect is particularly pronounced in uterine arteries, suggesting PGF contribution towards uterine vascular remodeling of pregnancy. These findings are consistent, utero-placental hypoperfusion and hypertension in preeclampsia patients is related with lower plasma PGF level; excessive sFlt-1 release binds to higher-than-normal amount of PGF, causing endothelial dysfunction in maternal tissue.[2,14,16]

Fusion and differentiation of trophoblasts occur through unknown mechanisms, but laboratory studies were able to mimic this process by treating placental villous explants and choriocarcinoma cell cultures with cAMP or forskolin. The studies showed upregulation of PGF by cAMP. In addition, VEGF expression is also upregulated by cAMP, although its expression pales in comparison with PGF expression. The later result might explain non-significant upregulation of VEGF during syncytialization process in the cDNA microarray studies. Circulating VEGF-A and PGF proteins are detectable in maternal serum as early as 8 weeks' gestation. Free serum PGF continues to increase during the course of pregnancy, but starts to decline at around 29 to 32 weeks of gestation.[8]

The cAMP is a strong activator of PGF expression in human trophoblasts through activation of PKA.[8,17] Other research indicates that the main target of PKA in the nucleus is CREB, which is phosphorylated on 133rd

serine residue. The serine phosphorylation allows interaction with the coactivator CBP/p300 and recruitment of the ternary transcription complex. Complicating the matter further, two functional CREs in the PGF has been identified; both are partly necessary for cAMP activation for PGF transcription.[18] Overexpression of a CREB-dominant negative mutant significantly inhibited forskolin-induced upregulation. Meanwhile, overexpression of wild-type CREB protein in JEG-3 cells only slightly increased forskolin-induced PGF. Recent discovery found GCM1-binding site lays approximately 230 bp upstream of the CRE motifs. GCM1 might be a target of PKA, since it was previously shown that cAMP enhanced GCM1 transcriptional activity and increased its interaction with CBP/p300.[8,17,18]

Interesting candidate ligands that could increase intracellular cAMP via GPCRs include calcitonin gene-related peptide (CGRP) and adrenomedullin (AM). Both molecules are expressed in the placenta and are known to affect vascular functions. Both ligands share a common membrane receptor: the calcitonin receptor-like receptor (CRLR), which is associated with specific receptor activity modifying proteins (RAMPs) and the G-protein complex8. The major cell signaling pathways involved during trophoblast invasion and migration are schematically described in Figure 10 above. Various mediators that are responsible for either promoting or inhibiting invasion/migration of trophoblast cells and activation of the respective signaling pathway(s).[9,19–21]

Mitogen-Activated Protein Kinases (MAPKs) Signaling Pathway

Ligand–receptor interaction activates receptor tyrosine kinases (RTKs) which phosphorylate tyrosine residues on the cytoplasmic domains of the receptor. Phosphorylated form of ERK1⁄2 was significantly higher in invasive trophoblast cells from normal pregnancy as compared to invasive trophoblast in placental bed biopsies from women with preeclampsia.[9,19]

Phosphoinositide 3-Kinase (PI3K)/AKT Signaling Pathway

PI3K/AKT signaling is associated with a variety of cellular processes including cell growth, proliferation, migration, and survival. After activation of RTKs or G- protein-coupled receptors (GPCRs), p85 and p110 subunits of PI3K are recruited to the membrane, respectively.[19,20]

JAK-STAT Signaling Pathway

Receptor aggregation by cytokine binding brings Janus kinases (JAKs, receptor-associated tyrosine kinases) in close proximity, enabling cross-phosphorylation of JAKs and cytoplasmic domains of the receptor. These phosphorylated domains can bind PTB domains or proteins possessing SH2-like signal transducer and activator of transcription (STATs) and phosphorylate them on specific tyrosine and serine residues (Fig. 11). Following activation, STATs dissociate from the respective ligands and translocate to nucleus as homo- or heterodimers where they bind to specific promoter sequences of the targeted genes, thereby regulating their transcription.[9,19]

Wnt Signaling Pathway

A recent study has also shown that canonical Wnt signaling plays a crucial role in EVT differentiation, promoting motility by upregulating the expression of promigratory genes[19,21], with result of trophoblast proliferation and invasion in pregnancy.

Focal Adhesion Molecules (FAKs) and Rho/ROCK Signaling Pathway

FAK signaling can be activated by integrin clustering, growth factors, and stimulus from GPCR. FAK has two prominent domains: a central kinase domain, which binds to integrin and activate other non- tyrosine receptor kinase; and c-terminal domain containing focal

adhesion targeting sequences, which bind integrin related proteins paxillin and talin.[19]

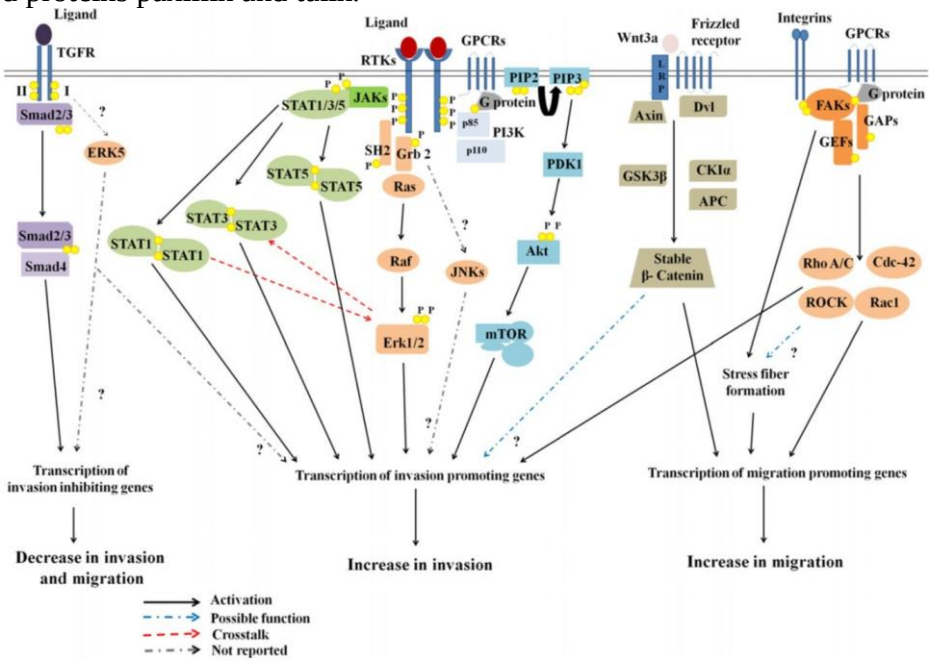


Figure 11. **Schematic representation of the signaling pathways activated during the invasion and migration of trophoblast cells.** Various cytokines and growth factors are known to activate Erk1⁄2, Akt, and STAT1, STAT3, and STAT5 during the process of trophoblast invasion. It has been shown that there is a cross talk between Erk1⁄2 and STAT1/STAT3 effecting each other's phosphorylation. Although reports indicate role of JNKs and ERK5 in placental development, but they have not been studied in context of trophoblast invasion and migration, whereas p38MAPK isnot involved. Smad2/3 is activated through TGFR and is known to negatively regulate trophoblast invasion. Wnt3a stimulates trophoblast cell migration and release of MMP-2, thus may have a role in invasion. FAK activation through integrin-mediated signaling plays an important role in trophoblast invasion and migration. Activation of FAK by various growth factors leads to RhoA/Rac1/cdc42/ROCK activation and stress fiber formation which increase migration of trophoblast cells. Cited from: Gupta SK, et al.[19]

TGF-beta Superfamily Signaling

Using explants culture of first-trimester chorionic villi, activin-A but not inhibin-A, stimulated the out-growth of the cytotrophoblast associated with increased expression of MMP-2 and MMP-9 suggesting that it has a role in promoting cytotrophoblast column formation during placentation19,22.

5. CONCLUSION

In short, our study shows relationship between PGF and preeclampsia by direct or indirect regulation of angiogenesis. PGF binding and activation of VEGFR-1 creates cascade of events necessary for trophoblast invasion, and disruption of PGF action may partially explain the preeclampsia.

REFERENCES

1. Pourroostaei Ardakani P, Ramezani A,Piravar Z, Asgharimoghadam N, Behzadi R, Jafari Fesharaki M. Different Polymorphisms of Placental Growth Factor (PLGF) Gene in Iranian Women's Population with Pre-eclampsia. Int J Cardiovasc Pract. 2019;4(4):111–6.
2. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia. CircRes. 2019 Mar 29;124(7):1094–112.
3. Manokhina I, Del Gobbo GF, Konwar C, Wilson SL, Robinson WP. Review:Placental biomarkers for assessing fetal health. Hum Mol Genet. 2017;26(R2):R237–45.

4. MacDonald TM, Walker SP, Hannan NJ, Tong S, Kaitu'u-Lino TJ. Clinical tools and biomarkers to predict preeclampsia. eBioMedicine. 2022 Jan;75:103780.
5. National Library of Medicine: National Center for Biotechnology Information. PGF placental growth factor [Homo sapiens (human)] [Internet]. 2023 [cited 2023 May 1]. Available from: https://www.ncbi.nlm.nih.gov/gene/5228
6. De Falco S. The discovery of placentagrowth factor and its biological activity. Exp Mol Med. 2012;44(1):1–9.
7. Ruggiero D, Nutile T, Nappo S, Tirozzi A, Bellenguez C, Leutenegger AL, et al. Genetics of PlGF plasma levels highlights a role of its receptors and supports the link between angiogenesis and immunity. Sci Rep. 2021;11(1):1–10.
8. Depoix C, Tee MK, Taylor RN. Molecular regulation of human placental growth factor (PLGF) gene expression in placental villi and trophoblast cells is mediated via the protein kinase A pathway. Reprod Sci. 2011;18(3):219–28.
9. Malik A, Pal R, Gupta SK. Interdependence of JAK-STAT and MAPK signaling pathways during EGF-mediated HTR-8/SVneo cell invasion. Yenugu S, editor. PLoS One.2017 May 25;12(5):e0178269.
10. Cunningham FG, Leveno KJ, Dashe JS, Hoffman BL, Spong CY, Casey BM. Williams Obstetrics. 26th ed.New York: McGraw-Hill; 2022.
11. Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive Value of the sFlt-1: PlGF Ratio in Women with Suspected Preeclampsia. N Engl J Med. 2016 Jan7;374(1):13–22.
12. Autiero M, Luttun A, Tjwa M, Carmeliet P. Placental growth factor and its receptor, vascular endothelial growth factor receptor-1: novel targetsfor stimulation of ischemic tissue revascularization and inhibition of angiogenic and inflammatory disorders. J Thromb Haemost. 2003Jul;1(7):1356–70.
13. Vogtmann R, Heupel J, Herse F, Matin M, Hagmann H, Bendix I, et al. Circulating Maternal sFLT1 (Soluble fms-Like Tyrosine Kinase-1) Is Sufficient to Impair Spiral Arterial Remodeling in a Preeclampsia Mouse Model. Hypertension. 2021 Oct;78(4):1067–79.
14. O'Brien M, Baczyk D, Kingdom JC. Endothelial Dysfunction in Severe Preeclampsia is Mediated by Soluble Factors, Rather than Extracellular Vesicles. Sci Rep. 2017 Jul 19;7(1):5887.
15. Chau K, Hennessy A, Makris A. Placental growth factor and pre- eclampsia. J Hum Hypertens. 2017 Dec 24;31(12):782–6.
16. Dewerchin M, Carmeliet P. PlGF: A multitasking cytokine with disease- restricted activity. Cold Spring Harb Perspect Med. 2012;2(8).
17. Gyselaers W. Preeclampsia Is a Syndrome with a Cascade of Pathophysiologic Events. J Clin Med. 2020 Jul 15;9(7):2245.
18. Mizuuchi M, Cindrova-Davies T, Olovsson M, Charnock-Jones DS, Burton GJ, Yung HW. Placental endoplasmic reticulum stress negatively regulates transcription ofplacental growth factor via ATF4 and ATF6β: implications for the pathophysiology of human pregnancy complications. J Pathol. 2016 Mar 12;238(4):550–61.
19. Gupta SK, Malhotra SS, Malik A, Verma S, Chaudhary P. Cell Signaling Pathways Involved During Invasion and Syncytialization of Trophoblast Cells. Am J Reprod Immunol. 2016 Mar;75(3):361–71.
20. Liu H, Yu L, Ding Y, Peng M, Deng Y. Progesterone Enhances the Invasion of Trophoblast Cells by Activating PI3K/AKT Signaling Pathway to Prevent Preeclampsia. CellTransplant. 2023 Jan; 32:096368972211456.
21. Zhang Z, Wang X, Zhang L, Shi Y, Wang J, Yan H. Wnt/β-catenin signaling pathway in trophoblasts and abnormal activation in preeclampsia. Mol Med Rep. 2017 Feb;16(2):1007– 13.
22. Yang D, Dai F, Yuan M, Zheng Y, Liu S, Deng Z, et al. Role of Transforming Growth Factor-β1 in Regulating Fetal- Maternal Immune Tolerance in Normal and Pathological Pregnancy. Front Immunol. 2021 Aug 31;12