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先兆子痫的发病机理与胎盘的相关性研究

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摘　要

先兆子痫(PE)为一种严重的妊娠并发症之一，通常在妊娠20周后开始，发病率为5%~7%，除典型的高血压和蛋白尿症状外常合并肝肾肺等器官功能受限，甚至死亡。该疾病可能与孕妇胎盘早期发育异常高度相关，包括：胎盘细胞滋养层的氧化还原状态、螺旋动脉的异常重塑及血管内皮细胞生长因子受体(Flt-1)水平增加等。上述三种因素互为因果，其中Flt-1已作为诊断PE的敏感指标。现有研究表明，Flt-1适量表达可能在PE妊娠中发挥保护作用，这为PE的治疗提供了新的思路。本文就PE的发病机理与胎盘的相关性研究作一综述。

关键词

先兆子痫，发病机理，胎盘

Study on the Relationship between the Pathogenesis of Preeclampsia and the Placenta

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Abstract

Preeclampsia (PE) is one of the serious pregnancy complications that usually begins after 20 weeks of gestation, with an incidence of 5%~7%. In addition to the typical symptoms of hypertension and proteinuria, it is often complicated by liver, kidney, lung and other organ function limitations, and

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even death. The disease may be highly associated with abnormal early placental development in pregnant women, including: redox status of placental cytotrophoblast, abnormal remodeling of spiral arteries, and increased levels of vascular endothelial growth factor receptor (Flt-1). The above three factors are mutually causal, and Flt-1 has been used as a sensitive indicator for the diagnosis of PE. Existing studies have shown that appropriate expression of Flt-1 may play a protective role in PE pregnancy, which provides a new idea for the treatment of PE. This paper reviews the correlation between the pathogenesis of PE and placenta.

Keywords

Preeclampsia, Pathogenesis, Placenta

1. 引言

先兆子痫(pre-eclampsia, PE)是指妊娠 20 周左右后，在高血压和蛋白尿的基础上出现眩晕、恶心和呕吐等症状，如未能及时治疗，孕妇会并发抽搐、肾衰竭、肺水肿及肝破裂等症状[1]，胎儿未来患心脑血管疾病的风险也会增加[2]，更甚者危及母胎生命，其总发病率占妊娠患者的 5%~7% [3]，并呈逐年上升的趋势，是我国孕产儿死亡的常见原因之一[4]。PE 是一种多因素复杂组合表现出来的疾病，可能与母亲遗传、免疫障碍、胎盘缺陷和外部环境等有关。其中胎盘因素可能为最关键原因[5]，由于胎盘细胞滋养层的氧化还原态可能导致螺旋动脉的异常重塑，从而造成血管内皮细胞生长因子受体(fms related tyrosine kinase 1, Flt-1)过度表达，三者相互作用、互为因果[5]。与正常妊娠孕妇相比，PE 患者在妊娠 30 周左右时 Flt-1 水平显着增加，这一水平也大于高血压妊娠孕妇，这表明 Flt-1 可作为诊断该疾病的敏感指标[6]，但 Flt-1 适量表达或许在 PE 妊娠中发挥保护作用[7]，这为临床诊治 PE 提供新的思路。PE 目前最有效的治疗方式任是提前终止妊娠，但这会导致早产儿的发生[8]。本文就 PE 的发病机理与胎盘的相关性研究作一综述。

2. PE 的发病机理

2.1. 胎盘细胞滋养层的氧化还原态

胎盘细胞滋养层的氧化还原态在调节妊娠期间的血压中起着举足轻重的作用。其原理是调节 KCa2.3 和 KCa3.1 的表达水平，从而影响血管内皮细胞收缩性，这与 KCa2.3 和 KCa3.1 是参与内皮细胞上控制血管收缩的 K^+重要通道有关[9]。K^+的正反馈作用可促进血管内皮细胞舒张，负反馈作用可导致血管收缩，从而造成血压升高[10]。在 PE 患者中，由于超氧化物歧化酶 (superoxide dismutase, SOD)负向调节和烟酰胺腺嘌呤二核苷酸磷酸氧化酶(nadph oxidase, NOX)正向调节导致 KCa 2.3 和 KCa 3.1 产生负反馈，血管内皮细胞开始收缩，最终高血压形成[11]。进一步研究还发现，PE 患者除 SOD、NOX 调节异常外，微量元素锶及尿酸水平均高于正常孕妇，导致细胞的氧化还原态发生改变，这表明锶也可能参与了 PE 的发生[12]。

2.2. 螺旋动脉的异常重塑

大多数研究认为当胎盘发生缺血或缺氧时，胎盘细胞滋养层处于氧化还原状态，如果发生在胎盘发育早期，可能导致胎盘和子宫壁之间螺旋动脉重塑受阻，造成其植入子宫肌层的深度不够[13]。这种胎盘与宫壁之间的血管结构异常严重时可使胎盘血流灌注减少，增加发生 PE 的风险[14]。进一步研究还证实，

由螺旋动脉重塑受损引起的胎盘缺血能导致 Flt-1 产生增加，进而引起孕妇血管内皮细胞收缩功能障碍，最后导致 PE [15]。

2.3. Flt-1

Flt-1 可以与游离于循环中的血管通透因子(vascular permeability factor, VPF)和胎盘生长因子(placental growth factor, PLGF)相结合，从而降低两者对血管内皮细胞收缩功能的影响[16]。适当的抑制血管内皮细胞的收缩性，在正常妊娠中是常见且可以接受的，但当过量的 Flt-1 表达会造成 PE 等严重后果[17]。此外，Jsa 等[17]研究发现，少部分的 Flt-1 水平增加不仅能减轻孕妇的心血管负荷，还能保护胎儿免受过量 VPF 的负面影响，这对母胎来说都是有益的。定期使用酶联免疫吸附测定试剂盒可以在体外定量测定孕妇血浆中 Flt-1 的浓度进行监测，可能是避免发生 PE 的有效方式[18]。对于已发生 PE 的孕妇控制 Flt-1 表达水平，未来可能是 PE 新的治疗方式[19]。同样，Sabah 等人[20]研究证实，妊娠期 Flt-1 的表达水平一般是非妊娠状态的 20-50 倍，保护胎盘免受 VPF、PLGF 等的侵袭，从而使胎盘附着于子宫肌层的适当深度。虽然 VPF 和 PlGF 在妊娠期间对胎儿的血管生成中起到积极作用，但由于胎盘缺血导致其表达失调刺激 Flt-1 的过度表达，反而会导致 PE [21]。但关于 Flt-1 何种表达水平是保护母胎或造成 PE，甚者对 PE 治疗有效，还需要进一步研究。

2.4. 其他因素

此外，许多其他因素如：血管紧张素 II1 型受体(AT1R)、炎症免疫过度激活、遗传因素、激素失调、神经递质水平、内皮素(ET-1)和蛋白质错误折叠等也可能在 PE 的发病机理中起作用。

3. PE 相关的胎盘动物模型

Fushima 等人[22]开发了一种新的小鼠 PE 胎盘模型，Flt-1 水平的过度表达，证实与胎盘缺血相关，从而引发母鼠血压升高和蛋白尿生成，以及子代的生长发育受限(intrauterine growth retardation, IUGR)。Huang 等人[23]在已建立的大鼠 PE 模型中使用戊四唑(PTZ)，揭示了炎症免疫过度激活在 PE 中的作用。Vogtmann 等人[24]在小鼠的 PE 胎盘模型中，使用强力霉素诱导 Flt-1 的重复表达，观察到诱导增强了小鼠胎盘血清可溶性血管内皮细胞生长因子受体 1 和信使核糖核酸水平，导致子代 IUGR 及母鼠典型的 PE 症状。此外，Saad 等人[25]在一项通过慢病毒载体介导的 Flt-1 特异性表达建立的小鼠 PE 模型中，普伐他汀组小鼠的胎盘蛋白浓度显着高于对照组($P < 0.05$)，这可能表明使用普伐他汀诱导胎盘产生 PLGF 在一定程度上可改善小鼠模型中的 PE 症状。

4. 治疗方式

尽管分娩胎盘是缓解 PE 患者高血压和蛋白尿的最优解决方案，但一些药物也能起到有效缓解 PE 症状或延长妊娠时间的作用。

一项诱导产生 PE 的大鼠模型中使用槲皮素(一种具有抗氧化和肾脏保护特性的生物类黄酮)联合阿司匹林的治疗效果的研究发现，该药物可降低 Flt-1 和 VPF 表达水平[26]。此外，用普伐他汀(一种降低坏胆固醇的首选药物)对 PE 小鼠模型进行治疗，可使 VPF 和 PlGF 水平升高，Flt-1 水平降低，从而可改善母鼠血压及促进子代生长发育[27]。

Yang 等人[26]研究发现，药物柳氮磺吡啶(一种抗炎和抗氧化剂)可减弱 PE 模型小鼠血浆和胎盘中脂质的过氧化表现、减少炎症细胞因子的产生及抑制 Flt-1 的表达，并增加胎盘中 PlGF 的分泌，与对照组相比明显提高了鼠崽的存活率($P < 0.05$)。此外，松弛素治疗 PE 的疗效的证明，该激素可降低大鼠血压和 Flt-1 水平[28]。

Gu 等人[29]的研究发现法舒地尔可以通过抑制信号通路来降低 Flt-1 水平，改善 PE 小鼠中的高血压症状。此外，关于二甲双胍的研究表明[30]，其能减少 Flt-1 的产生，并通过对线粒体的影响来改善内皮功能障碍，从而预防 PE 的发生。另一项关于 PE 小鼠模型的研究表明，使用普伐他汀对母鼠进行治疗可促进子代大脑及骨骼的生长发育[25]。

5. 展望

尽管初步研究表明，降低 Flt1 在妊娠中的表达水平可改善 PE 的症状及降低 IUGR 的发生风险[31]，但如何维持在一个合适的水平使其达到微妙的平衡还需要进一步研究，因为适量的 Flt1 表达在保护胎儿方面也起着至关重要的作用[32]。因此监测 Flt1 表达水平在预防和改善 PE 症状等方面具有重大潜力，未来我们需要在这个方向进行更深入的研究。

参考文献

[1] Kaya, G.D. (2021) A Complex Pregnancy: Preeclampsia. *Webinar on Pediatrics, Nursing Care, CAM Therapies and Immunology Research*, Vienna.

[2] Giannakou, K. (2021) Prediction of Pre-Eclampsia. *Obstetric Medicine*, **14**, 220-224.

[3] Rana, S., Lemoine, E., Granger, J.P. and Karumanchi, A. (2019) Preeclampsia: Pathophysiology, Challenges, and Perspectives. *Circulation Research*, **124**, 1094-1112. https://doi.org/10.1161/CIRCRESAHA.118.313276

[4] 吕鑫，张为远，张靖霄，等. 早发与晚发子痫前期高危因素的对比分析[J]. 中华妇产科杂志，2021，56(11): 760-766.

[5] Hu, M., Li, J., Baker, P.N., *et al*. (2021) Revisiting Preeclampsia: A Metabolic Disorder of the Placenta. *The FEBS Journal*, **289**, 336-354. https://doi.org/10.1111/febs.15745

[6] Amin, A., El-Deen, I.M., Seleem, A., *et al*. (2020) A Comparative Study: Gene Expression VEGF, FLT-1 and KDR and Level of PLGF in Preeclampsia and Normal Pregnancy. *Alfarama Journal of Basic & Applied Sciences*, **2**, 8-15. https://doi.org/10.21608/ajbas.2020.37520.1028

[7] Sahu, M.B., Deepak, V., Gonzales, S.K., Rimawi, B.H., Watkins, K.K., Smith, A.K., Badell, M.L., Sidell, N. and Rajakumar, A. (2018) Decidual Cells from Women with Preeclampsia Exhibit Inadequate Decidualization and Reduced sFlt1 Suppression. *Pregnancy Hypertension*, **15**, 64-71. https://doi.org/10.1016/j.preghy.2018.11.003

[8] 王莉，赵霞，吴莎，等. 妊娠期高血压疾病 300 例妊娠结局分析[J]. 中国实用妇科与产科杂志，2021，37(5): 588-591.

[9] Choi, S., Kim, J.A., Li, H.-Y., Lee, S.-J., Seok, Y.S., Kim, T.H., Han, K.-H., Park, M.H., Cho, G.J. and Suh, S.H. (2019) Altered Redox State Modulates Endothelial KCa2.3 and KCa3.1 Levels in Normal Pregnancy and Preeclampsia. *Antioxidants & Redox Signaling*, **30**, 505-519. https://doi.org/10.1089/ars.2017.7038

[10] Brähler, S., Kaistha, A., Schmidt, V.J., Wölfle, S.E., Busch, C., Kaistha, B.P., Kacik, M., Hasenau, A.-L., Grgic, I., Si, H., *et al*. (2009) Genetic Deficit of SK3 and IK1 Channels Disrupts the Endothelium-Derived Hyperpolarizing Factor Vasodilator Pathway and Causes Hypertension. *Circulation*, **119**, 2323-2332. https://doi.org/10.1161/CIRCULATIONAHA.108.846634

[11] Si, H., Heyken, W.-T., Wölfle, S.E., Tysiac, M., Schubert, R., Grgic, I., Vilianovich, L., Giebing, G., Maier, T., Gross, V., *et al*. (2006) Impaired Endothelium-Derived Hyperpolarizing Factor-Mediated Dilations and Increased Blood Pressure in Mice Deficient of the Intermediate-Conductance Ca^{2+}-Activated K^{+} Channel. *Circulation Research*, **99**, 537-544. https://doi.org/10.1161/01.RES.0000238377.08219.0c

[12] Barneo-Caragol, C., Martínez-Morillo, E., Rodríguez-González, S., Lequerica-Fernández, P., Vega-Naredo, I. and Alvarez, F.V. (2019) Increased Serum Strontium Levels and Altered Oxidative Stress Status in Early-Onset Preeclampsia. *Free Radical Biology & Medicine*, **138**, 1-9. https://doi.org/10.1016/j.freeradbiomed.2019.05.001

[13] Vaka, V.R., McMaster, K.M., Cunningham, M.W., Ibrahim, T., Hazlewood, R., Usry, N., Cornelius, D.C., Amaral, L.M. and Lamarca, B.D. (2018) Role of Mitochondrial Dysfunction and Reactive Oxygen Species in Mediating Hypertension in the Reduced Uterine Perfusion Pressure Rat Model of Preeclampsia. *Hypertension*, **72**, 703-711. https://doi.org/10.1161/HYPERTENSIONAHA.118.11290

[14] Wu, J.N., Ren, Y.Y., Zhu, C., *et al*. (2021) Abnormal Placental Perfusion and the Risk of Stillbirth: A Hospital-Based Retrospective Cohort Study. *BMC Pregnancy and Childbirth*, **21**, Article No. 308. https://doi.org/10.1186/s12884-021-03776-8

[15] Vrooman, L.A., Rhon-Calderon, E.A., Chao, O.Y., *et al*. (2020) Assisted Reproductive Technologies Induce Temporally Specific Placental Defects and the Preeclampsia Risk marker sFLT1 in Mouse. *Development*, **147**, dev186551. https://doi.org/10.1242/dev.186551

[16] McMahon, K., Karumanchi, S.A., Stillman, I.E., Cummings, P., Patton, D. and Easterling, T. (2014) Does Soluble FMS-Like Tyrosine Kinase-1 Regulate Placental Invasion? Insight from the Invasive Placenta. *American Journal of Obstetrics & Gynecology*, **210**, 68.e1-68.e4. https://doi.org/10.1016/j.ajog.2013.08.032

[17] Jsa, B., Saa, B., Hr, A., *et al*. (2020) Hydrogen Sulfide Releasing Molecule MZe786 Inhibits Soluble Flt-1 and Prevents Preeclampsia in a Refined Mouse RUPP Model. *Redox Biology*, **38**, Article ID: 101814.

[18] Chielie, K.A., Dhingra, R. and Bhatla, N. (2020) Estimation of Serum Levels of VEGF & SVEGFR-1 (sFLT-1) in Preeclampsia. *Journal of Evolution of Medical and Dental Sciences*, **9**, 913-918. https://doi.org/10.14260/jemds/2020/197

[19] Shibuya, M., Matsui, H., Sasagawa, T., *et al*. (2021) A Simple Detection Method for the Serum sFLT1 Protein in Preeclampsia. *Scientific Reports*, **11**, Article No. 20613. https://doi.org/10.1038/s41598-021-00152-6

[20] Sabah, F., Usman, Z.M., Sheikh, M.A., *et al*. (2020) Association of Resolvin Level in Pregnant Women with Preeclampsia and Metabolic Syndrome. *Taiwanese Journal of Obstetrics & Gynecology*, **59**, 105-108. https://doi.org/10.1016/j.tjog.2019.11.016

[21] Parchem, J.G., Kanasaki, K., Kanasaki, M., Sugimoto, H., Xie, L., Hamano, Y., Lee, S.B., Gattone, V.H., Parry, S., Strauss, J.F., *et al*. (2018) Loss of Placental Growth Factor Ameliorates Maternal Hypertension and Preeclampsia in Mice. *The Journal of Clinical Investigation*, **128**, 5008-5017. https://doi.org/10.1172/JCI99026

[22] Fushima, T., Sekimoto, A., Minato, T., Ito, T., Oe, Y., Kisu, K., Sato, E., Funamoto, K., Hayase, T., Kimura, Y., *et al*. (2016) Reduced Uterine Perfusion Pressure (RUPP) Model of Preeclampsia in Mice. *PLOS ONE*, **11**, e0155426. https://doi.org/10.1371/journal.pone.0155426

[23] Huang, Q., Liu, L., Hu, B., Di, X., Brennecke, S. and Liu, H. (2014) Decreased Seizure Threshold in an Eclampsia-Like Model Induced in Pregnant Rats with Lipopolysaccharide and Pentylenetetrazol Treatments. *PLOS ONE*, **9**, e89333. https://doi.org/10.1371/journal.pone.0089333

[24] Vogtmann, R., Kühnel, E., Dicke, N., Verkaik-Schakel, R.N., Plösch, T., Schorle, H., Stojanovska, V., Herse, F., Köninger, A., Kimmig, R., *et al*. (2019) Human sFLT1 Leads to Severe Changes in Placental Differentiation and Vascularization in a Transgenic hsFLT1/rtTA FGR Mouse Model. *Frontiers in Endocrinology* (*Lausanne*), **10**, Article No. 165.

[25] Saad, A.F., Kechichian, T., Yin, H., Sbrana, E., Longo, M., Wen, M., Tamayo, E., Hankins, G.D.V., Saade, G.R. and Costantine, M.M. (2013) Effects of Pravastatin on Angiogenic and Placental Hypoxic Imbalance in a Mouse Model of Preeclampsia. *Reproductive Sciences*, **21**, 138-145. https://doi.org/10.1177/1933719113492207

[26] Yang, S., Song, L., Shi, X., Zhao, N. and Ma, Y. (2019) Ameliorative Effects of Pre-Eclampsia by Quercetin Supplement to Aspirin in a Rat Model Induced by L-NAME. *Biomedicine & Pharmacotherapy*, **116**, Article ID: 108969. https://doi.org/10.1016/j.biopha.2019.108969

[27] Fox, K., Longo, M., Tamayo, E., Kechichian, T., Bytautiene, E., Hankins, G.D., Saade, G. and Costantine, M.M. (2011) Effects of Pravastatin on Mediators of Vascular Function in a Mouse Model of Soluble FMS-Like Tyrosine Kinase-1-Induced Preeclampsia. *American Journal of Obstetrics & Gynecology*, **205**, 366.e1-366.e5. https://doi.org/10.1016/j.ajog.2011.06.083

[28] Brownfoot, F.C., Hannan, N.J., Cannon, P., Nguyen, V., Hastie, R., Parry, L.J., Senadheera, S., Tuohey, L., Tong, S. and Kaitu'U-Lino, T.J. (2019) Sulfasalazine Reduces Placental Secretion of Antiangiogenic Factors, Up-Regulates the Secretion of Placental Growth Factor and Rescues Endothelial Dysfunction. *EBioMedicine*, **41**, 636-648. https://doi.org/10.1016/j.ebiom.2019.02.013

[29] Gu, Y., Feng, Y., Yu, J., Yuan, H., Yin, Y., Ding, J., Zhao, J., Xu, Y., Xu, J. and Che, H. (2017) Fasudil Attenuates Soluble FMS-Like Tyrosine Kinase-1 (sFlt-1)-Induced Hypertension in Pregnant Mice through RhoA/ROCK Pathway. *Oncotarget*, **8**, 104104-104112. https://doi.org/10.18632/oncotarget.22017

[30] Romero, R., Erez, O., Hüttemann, M., Maymon, E., Panaitescu, B., Conde-Agudelo, A., Pacora, P., Yoon, B.H. and Grossman, L.I. (2017) Metformin, the Aspirin of the 21st Century: Its Role in Gestational Diabetes Mellitus, Prevention of Preeclampsia and Cancer, and the Promotion of Longevity. *American Journal of Obstetrics & Gynecology*, **217**, 282-302. https://doi.org/10.1016/j.ajog.2017.06.003

[31] Birdir, C., Droste, L., Fox, L., *et al*. (2018) Predictive Value of sFlt-1, PlGF, sFlt-1/PlGF Ratio and PAPP-A for Late-Onset Preeclampsia and IUGR between 32 and 37 Weeks of Pregnancy. *Pregnancy Hypertension*, **12**, 124-128. https://doi.org/10.1016/j.preghy.2018.04.010

[32] Alahakoon, T.I., Medbury, H., Williams, H., *et al*. (2019) Maternal Flt-1 and Endoglin Expression by Circulating Monocyte Subtype and Polarization in Preeclampsia and Fetal Growth Restriction. *European Journal of Obstetrics, Gynecology and Reproductive Biology*: *X*, **3**, Article ID: 100024. https://doi.org/10.1016/j.eurox.2019.100024