周 產 期 會 訊

中華民國周產期醫學會會訊　第五十一期　2000 年 4 月

發行人：楊勉力　會訊主編：張舜智

秘書長：劉瑞德

會　址：台北市常德街 1 號　電話：(02)23816198　傳真：(02)23814234

CURRENT PERSPECTIVES OF PREECLAMPSIA (II)

Tzu-Hao Wang, M.D., Ph.D.

Department of Obstetrics and Gynecology, Chang-Gung Memorial Hospital, Lin-Kou Medical Center, Tao-Yuan, TAIWAN

Signal transduction pathways in preeclamptic placentae

Appropriate cross-talk between endometrium and placenta is critical for normal pregnancy. For instance, cytotrophoblasts expressing □4 integrins bind immobilized VCAM-1 *in vitro*, suggesting that this receptor-pair could mediate cytotrophoblast-endothelium or cytotrophoblast-cytotrophoblast interactions *in vivo*, during endovascular invasion. On the other hand in preeclampsia, in which endovascular invasion remains superficial, cytotrophoblasts fail to express most of these endothelial markers (31), suggesting that this adhesion phenotype switch is required for successful endovascular invasion and normal placentation (32). Placental TGF-□3 expression is high in early pregnancy but falls at around 9 weeks' gestation. A failure to downregulate expression of TGF-□3 at around 9 weeks' gestation results in shallow trophoblast invasion and predisposes the pregnancy to preeclampsia (12).

Placenta growth factor (PlGF), a member of the VEGF family of angiogenic factors, is prominently expressed by trophoblast. Decreased levels PlGF during preeclampsia could influence endothelial cell and trophoblast function, thereby contributing to the pathogenesis of the disease (5). Recombinant human vascular endothelial growth factor (VEGF) has been demonstrated to activate c-Jun N-terminal kinase (JNK) in the normal trophoblast through flt-1 receptors. JNK has been shown to be associated with apoptosis and other functions (33-35). Trophoblast-derived VEGF/PIGF could act in a paracrine fashion to promote uterine angiogenesis and vascular permeability within the placental bed. In addition, presence of functional receptors for VEGF/PlGF on normal trophoblast suggests that VEGF/PIGF functions in an autocrine manner to perform an as yet undefined role in trophoblast invasion, differentiation, and/or metabolic activity during placentation (11).

Flt-1 is the receptor for PlGF. Presence of Flt-1 on trophoblast suggests that PlGF also have an autocrine role(s) in regulating trophoblast function in addition to its role as a paracrine angiogenic factor within the placenta and endometrium. Exogenous PlGF induced specific activation of the stress-activated protein kinase (SAPK) pathways, JNK and p38 kinase, in primary term trophoblast with little to no induction of the extracellular signal regulated kinase (ERK-1 and -2) pathways, providing a direct evidence of a biochemical and functional role for PlGF/Flt-1 in normal trophoblast. Collectively, aberrant PlGF expression during pregnancy may impact upon trophoblast function as well as vascularity within the placental bed (13), accounting for the pathogenesis of preeclampsia (5).

REFERENCES

1. C**unningham FG, MacDonald PC, Gant NF, et al.** Chapter 31. Hypertensive disorders in pregnancy. *Williams Obstetrics*. 20th ed. Stamford, Connecticut: Appleton and Lange; 1997:693-744.
2. **Duley L.** Maternal mortality associated with hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. *Br J Obstet Gynaecol*. 1992;99:547-53.
3. **Broughton Pipkin F.** What Is the Place of Genetics in the Pathogenesis of Pre-Eclampsia? *Biol Neonate*. 1999;76:325-330.
4. **Khong TY, De Wolf F, Robertson WB, Brosens I.** Inadequate maternal vascular response to placentation in pregnancies complicated by pre-eclampsia and by small-for-gestational age infants. *Br J Obstet Gynaecol*. 1986;93:1049-59.
5. **Torry DS, Wang HS, Wang TH, Caudle MR, Torry RJ.** Preeclampsia is associated with reduced serum levels of placenta growth factor. *Am J Obstet Gynecol*. 1998;179:1539-44.
6. **Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK.** Preeclampsia: an endothelial cell disorder. *Am J Obstet Gynecol*. 1989;161:1200-4.
7. **Stallmach T, Hebisch G, Orban P, Lu X.** Aberrant positioning of trophoblast and lymphocytes in the feto- maternal interface with pre-eclampsia. *Virchows Arch*. 1999;434:207-11.
8. **Hennessy A, Pilmore HL, Simmons LA, Painter DM.** A deficiency of placental IL-10 in preeclampsia. *J Immunol*. 1999;163:3491-5.
9. **Dekker GA, Sibai BM.** Etiology and pathogenesis of preeclampsia: current concepts. *Am J Obstet Gynecol*. 1998;179:1359-75.

10. **DiFederico E, Genbacev O, Fisher SJ.** Preeclampsia is associated with widespread apoptosis of placental cytotrophoblasts within the uterine wall. *Am J Pathol*. 1999;155:293-301.
11. **Shore VH, Wang TH, Wang CL, Torry RJ, Caudle MR, Torry DS.** Vascular endothelial growth factor, placenta growth factor and their receptors in isolated human trophoblast. *Placenta*. 1997;18:657-65.
12. **Caniggia I, Grisaru-Gravnosky S, Kuliszewsky M, Post M, Lye SJ.** Inhibition of TGF-beta 3 restores the invasive capability of extravillous trophoblasts in preeclamptic pregnancies. *J Clin Invest*. 1999;103:1641-50.
13. **Desai J, Holt-Shore V, Torry RJ, Caudle MR, Torry DS.** Signal transduction and biological function of placenta growth factor in primary human trophoblast. *Biol Reprod*. 1999;60:887-92.
14. **Benyo DF, Miles TM, Conrad KP.** Hypoxia stimulates cytokine production by villous explants from the human placenta. *J Clin Endocrinol Metab*. 1997;82:1582-8.
15. **Mise H, Sagawa N, Matsumoto T, et al.** Augmented placental production of leptin in preeclampsia: possible involvement of placental hypoxia. *J Clin Endocrinol Metab*. 1998;83:3225-9.
16. **Wang TH, Wang HS.** Apoptosis: (1). Overview and clinical significance. *J Formos Med Assoc*. 1999;98:381-93.
17. **Wang TH, Wang HS.** Apoptosis: (2) characteristics of apoptosis. *J Formos Med Assoc*. 1999;98:531-42.
18. **Lea RG, Tulppala M, Critchley HO.** Deficient syncytiotrophoblast tumour necrosis factor-alpha characterizes failing first trimester pregnancies in a subgroup of recurrent miscarriage patients. *Hum Reprod*. 1997;12:1313-20.
19. **Lea RG, al-Sharekh N, Tulppala M, Critchley HO.** The immunolocalization of bcl-2 at the maternal-fetal interface in healthy and failing pregnancies. *Hum Reprod*. 1997;12:153-8.
20. **Al-Lamki RS, Skepper JN, Loke YW, King A, Burton GJ.** Apoptosis in the early human placental bed and its discrimination from necrosis using the in-situ DNA ligation technique. *Hum Reprod*. 1998;13:3511-9.
21. **Ashkenazi A, Dixit VM.** Death receptors: signaling and modulation. *Science*. 1998;281:1305-8.
22. **Payne SG, Smith SC, Davidge ST, Baker PN, Guilbert LJ.** Death receptor Fas/Apo-1/CD95 expressed by human placental cytotrophoblasts does not mediate apoptosis. *Biol Reprod*. 1999;60:1144-50.

23. **Knofler M, Stenzel M, Husslein P.** Shedding of tumour necrosis factor receptors from purified villous term trophoblasts and cytotrophoblastic BeWo cells. *Hum Reprod*. 1998;13:2308-16.
24. **Uckan D, Steele A, Cherry, et al.** Trophoblasts express Fas ligand: a proposed mechanism for immune privilege in placenta and maternal invasion. *Mol Hum Reprod*. 1997;3:655-62.
25. **Torry DS, Ahn H, Barnes EL, Torry RJ.** Placenta growth factor: potential role in pregnancy. *Am J Reprod Immunol*. 1999;41:79-85.
26. **Franke TF, Kaplan DR, Cantley LC, Toker A.** Direct regulation of the Akt proto-oncogene product by phosphatidylinositol-3,4-bisphosphate. *Science*. 1997;275:665-8.
27. **Franke TF, Kaplan DR, Cantley LC.** PI3K: downstream AKTion blocks apoptosis. *Cell*. 1997;88:435-7.
28. **Franke TF, Cantley LC.** Apoptosis. A Bad kinase makes good. *Nature*. 1997;390:116-7.
29. **Gerber HP, McMurtrey A, Kowalski J, et al.** Vascular endothelial growth factor regulates endothelial cell survival through the phosphatidylinositol 3'-kinase/Akt signal transduction pathway. Requirement for Flk-1/KDR activation. *J Biol Chem*. 1998;273:30336-43.
30. **Gerber HP, Dixit V, Ferrara N.** Vascular endothelial growth factor induces expression of the antiapoptotic proteins Bcl-2 and A1 in vascular endothelial cells. *J Biol Chem*. 1998;273:13313-6.
31. **Zhou Y, Damsky CH, Fisher SJ.** Preeclampsia is associated with failure of human cytotrophoblasts to mimic a vascular adhesion phenotype. One cause of defective endovascular invasion in this syndrome?. *J Clin Invest*. 1997;99:2152-64.
32. **Zhou Y, Fisher SJ, Janatpour M, et al.** Human cytotrophoblasts adopt a vascular phenotype as they differentiate. A strategy for successful endovascular invasion? *J Clin Invest*. 1997;99:2139-51.
33. **Wang TH, Wang HS, Ichijo H, et al.** Microtubule-interfering agents activate c-Jun N-terminal kinase/stress- activated protein kinase through both Ras and apoptosis signal- regulating kinase pathways. *J Biol Chem*. 1998;273:4928-36.
34. **Wang TH, Popp DM, Wang HS, et al.** Microtubule dysfunction induced by paclitaxel initiates apoptosis through both c-Jun N-terminal kinase (JNK)-dependent and -independent pathways in ovarian cancer cells. *J Biol Chem*. 1999;274:8208-16.
35. **Wang TH, Wang HS, Soong YK.** Regulation and functions of c-Jun N-terminal kinase/stress-activated protein kinase. *Chang Gung Med J*. 2000;23:57-72.