

Editorial

Endothelial cell dysfunction and preeclampsia



Preeclampsia is a pregnancy-specific syndrome of hypertension and proteinuria and one of the leading causes of perinatal morbidity and mortality.¹ The pathogenesis of preeclampsia, although not entirely clear, is typically abnormal placental implantation, followed by endothelial dysfunction with subsequently resulting vasospasm, coagulopathy, or changes in capillary permeability; this underscores the importance of successfully established circulation networks between the fetus and mother.¹ These established circulation networks require an ongoing sequential process, and one of the most noteworthy facilitators of this process is the success of angiogenesis. However, angiogenesis is a very complicated procedure because normal physiological function is needed, and many diverse pathologies and disease status indicators also involve an active angiogenesis process.² Endothelial progenitor cells (EPCs) were characterized and isolated from peripheral blood by Asahara et al³ in 1997, and are recruited to vascular lesion sites. EPCs may play a critical role in the repair of blood vessel damage, restoration of endothelial function, or neoangiogenesis after the fetal period.⁴ Dysfunction of endothelial cells is a hallmark of many cardiovascular diseases,⁵ and there is evidence that reductions in the number and functionality of circulating EPCs might contribute to adult cardiovascular disease.³ However, the role of circulating EPCs on the development of preeclampsia is not conclusive.

The study by Parsanezhad et al⁶ in this issue of the *Journal of the Chinese Medical Association* seems to be the first report to study the differences between three distinct subsets of EPCs of maternal peripheral blood, including circulating angiogenic cells (CAC), colony-forming unit endothelial cells (CFU-ECs), and endothelial colony-forming cells (ECFCs) in women with and without preeclampsia. They show higher numbers of CACs and ECFCs subsets in the peripheral blood but fewer colony formation capacities in the peripheral blood of pregnant women with preeclampsia compared with that of women with normal pregnancy, suggesting that the functionality of CACs and ECFCs in women with preeclampsia was decreased. By contrast, the number of CACs increases without alternations in colony formation ability was found in women with normal pregnancy.⁶

It is unclear why the high numbers of ECFCs in the peripheral blood of women with preeclampsia did not contribute to an elevated number of colony formations, suggesting that ECFCs of women with and without preeclampsia might

be different in the phenotype. Unfortunately, the authors failed to provide any additional evidence to support their findings. In addition to the measurement of ECFC levels in the peripheral blood of pregnant women with and without preeclampsia, the following strategies might be required to characterize ECFC phenotype, including investigation of cloning-forming ability, proliferation, and migration toward vascular endothelial growth factor-A and fibroblast growth factor-2, *in vitro* formation of capillary-like structures, and *in vivo* vasculogenic ability in immunodeficient mice. Without the aforementioned experiments, the authors' claim that ECFCs in preeclampsia have lost their functional capabilities is overestimated.⁶ Therefore, it is reasonable to suspend the aforementioned conclusion. ECFCs are a subset of circulating endothelial progenitor cells that participate in the formation of vasculature during development.⁷ It is hard to believe that the absolute number of ECFCs in the peripheral blood of pregnant women with preeclampsia is increased compared with that of women without preeclampsia. A recent study from Muñoz-Hernandez and colleagues⁷ did not find any statistically significant difference of phenotypic and functional characteristics of cord blood ECFCs between pregnant women with and without preeclampsia. By contrast, the ECFC level in preeclampsia was statistically lower than in the control, with a median abundance of 1 colony per 10 mL of cord blood and a 25th to 75th interquartile range of 0 to 4 colonies per 10 mL of cord blood.⁷ In addition, a significant portion of the women with preeclampsia in their study had no measurable ECFCs.⁷ This finding was consistent after adjustment of most obstetric factors, suggesting that level of ECFCs was an independent factor in preeclampsia.⁷

Moreover, recent studies have shown many important confounding factors on circulating levels of ECFCs, including body mass index and gestational age.⁸ Furthermore, Yoder and colleagues⁹ demonstrated that early endothelial progenitor cells that generate endothelial cell colony-forming units are hematopoietic in origin, fail to form perfused vessels *in vivo*, and are clonally distinct from ECFCs; thus, in addition to variations in the number of AC133+/KDR+/CD34+ endothelial progenitor cells, which are distinguished from ECFCs, it remains unclear whether preeclampsia altered baseline levels in the peripheral blood ECFCs. The more unambiguously identified ECFCs, based on well-known endothelial markers and functional properties, may be needed to confirm the levels or roles of

circulating ECFCs in the peripheral blood of pregnant women with preeclampsia, because many biomarkers have been used in an attempt to provide a much more effective tool in predicting the risk of occurrence of preeclampsia.¹⁰

Conflicts of interest

The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

Acknowledgments

This work was supported in part by a grant from the Ministry of Science and Technology, Executive Yuan (MOST 103-2314-B-010 -043 -MY3), and Taipei Veterans General Hospital (V103C-112, V104C-095 and V103E4-003), Taipei, Taiwan, R.O.C.

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