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Letter to the Editor

Padma Murthi, PhD[1,2] and Bill Kalionis, PhD[1,2]

We read with interest the article by Sun et al[1] that described the regulation of epithelial–mesenchymal transition (EMT) by homeobox gene *DLX4* in JEG-3 trophoblast cells and its potential role in preeclampsia. We would like to bring to the attention of the authors and the readers the concerns we have regarding the nature of the samples analyzed in this study and the interpretation of some of the results.

Sun et al[1] correctly described the EMT that occurs in the extravillous trophoblast cell columns in the placental bed. The placental bed consists of the part of the uterine wall after delivery to which the placenta was attached and is comprised of extravillous trophoblast and decidua or myometrium.[2] Therefore, gene expression changes due to abnormal EMT in placental pathologies such as preeclampsia should be detected in the placental bed and not in the free-floating chorionic villi of the placenta.

In this study,[1] on page 1139, the authors described the sample collection procedure as "Placental samples were randomly obtained from the central areas of the fresh placental cotyledon, and the attached deciduas were carefully removed." In carrying out this procedure, the authors removed a substantial portion, if not all, of the remaining attached placental bed and decidua from third trimester preeclampsia and control placentae. The bulk of the sample after removal of the decidua and underlying cells would comprise the free-floating chorionic villous tissue.

In previous publications, we showed that *DLX4* is expressed in the chorionic villi in syncytiotrophoblasts, cytotrophoblast cells, and in the endothelial cells of term fetal growth restriction-affected placentae.[3,4] Indeed, Sun et al[5] also showed that *DLX4* was expressed in chorionic villous tissue in samples that were prepared in a very similar manner to that described in Sun et al.[1]

Thus, in Figures 1 and 2 of Sun et al,[1] the signals are most likely due to the expression of *DLX4* in the chorionic villi. The contribution of any small portion of the placental bed that might still remain attached to the villi after removal of the decidua and underlying cells would be very small. To our knowledge, there is no evidence of EMT within the chorionic villi. A more likely explanation for the differences seen between the levels of *DLX4* in preeclampsia-affected placentas and gestational age-matched controls, in Figures 1 and 2, are the differences in apoptosis levels, which were shown to be controlled by *DLX4* in villous trophoblast cells in the previous publication by Sun et al.[5]

In summary, we contend that the conclusions regarding the contribution of *DLX4* to EMT in preeclampsia and gestation-matched control placental tissues cannot be made with the methodology used by Sun et al[1] and consequently, the data presented in Figures 1 and 2 cannot be attributed to differences in *DLX4* expression levels in the extravillous cytotrophoblast columns where EMT occurs.

Declaration of Conflicting Interests

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[1] Department of Perinatal Medicine Pregnancy Research Centre, The Royal Women's Hospital, Parkville, Victoria, Australia
[2] Department of Obstetrics and Gynaecology, University of Melbourne, Parkville, Victoria, Australia

Corresponding Author:
Padma Murthi, Department of Perinatal Medicine Pregnancy Research Centre, The Royal Women's Hospital, 20 Flemington Road, Parkville 3052, Australia
Email: padma@unimelb.edu.au