

Editorial: Mechanisms Safeguarding the Trophoblast Multipotent State

Rajesh Kumar, PhD

Dana-Farber Cancer Institute, Boston, Massachusetts, 02140 USA.

Email: rajesh_kumar@dfci.harvard.edu

Approximately one-third of the human pregnancies have placenta-related defects including recurrent miscarriage, preeclampsia, fetal growth restriction, and uterine inflammation (Young, Levine et al. 2010, Giakoumopoulos and Golos 2013, James, Srinivasan et al. 2014). Hence it is very important to understand the pathophysiology of placental development. Pregnancy is a unique situation in which the mother and the hemi allogeneic fetus cordially coexist. Several fetal, maternal and placental mechanisms function in concert to protect the fetus from immunological recognition and rejection (PrabhuDas, Bonney et al. 2015). The placenta provides the interface for gas and nutrient exchange between the mother and the fetus and hence proper placental function is critical for healthy pregnancy. However, despite its role in sustaining pregnancy, the trophoblast stem and progenitor cells hierarchy and the underlying molecular mechanisms responsible for the development of the placenta are not well described. Recent advancement in the embryonic stem cells (ESCs)/trophoblast stem cells (TSCs) research led to better understanding of their regulation in terms of transcription networks, cell signaling pathways and epigenetic modifiers (Natale, Schweitzer et al. 2017, Yang, Liu et al. 2017, Nandi, Lim et al. 2018, Okae, Toh et al. 2018). In this issue of the Postdoc [Journal](#), Chrysanthou and colleague described the critical role and mechanisms safeguarding the trophoblast multipotent state. Authors highlighted genes and signaling pathways with significant relevance in the maintenance of the trophoblast multipotent state and differentiation; namely

Tead4.

Cdx2, Hippo, Yap1, Eomes, Esrrb, Elf5, Ap-2 γ (Tcfap2c), Sox2, Fgf signaling, and Tgf- β . And the importance of these genes has been broadly described in this issue. Epigenetic regulation of the trophoblast lineage-specific transcription factors controls various differentiation-related and physiological processes in trophoblast via imprinting-dependent and -independent mechanisms (Branco, King et al. 2016). Chrysanthou and colleague have elegantly described the intriguing aspect of TSC lineage restriction, maintenance of the trophoblast stem cell state, subtype specialization and differentiation.

References:

- Branco, M. R., M. King, V. Perez-Garcia, A. B. Bogutz, M. Caley, E. Fineberg, L. Lefebvre, S. J. Cook, W. Dean, M. Hemberger and W. Reik (2016). "Maternal DNA Methylation Regulates Early Trophoblast Development." *Dev Cell* 36(2): 152-163.
<https://doi.org/10.1016/j.devcel.2015.12.027>
PMid:26812015 PMCid:PMC4729543
- Giakoumopoulos, M. and T. G. Golos (2013). "Embryonic stem cell-derived trophoblast differentiation: a comparative review of the biology, function, and signaling mechanisms." *J Endocrinol* 216(3): R33-45.
<https://doi.org/10.1530/JOE-12-0433>
PMid:23291503 PMCid:PMC3809013
- James, J. L., S. Srinivasan, M. Alexander and L. W. Chamley (2014). "Can we fix it? Evaluating the potential of placental stem cells for the treatment of pregnancy disorders." *Placenta* 35(2): 77-84.

<https://doi.org/10.1016/j.placenta.2013.12.010> PMID:24406265

Nandi, P., H. Lim, E. J. Torres-Garcia and P. K. Lala (2018). "Human trophoblast stem cell self-renewal and differentiation: Role of decorin." *Sci Rep* 8(1): 8977. <https://doi.org/10.1038/s41598-018-27119-4> PMID:29895842 PMCid:PMC5997742

Natale, B. V., C. Schweitzer, M. Hughes, M. A. Globisch, R. Kotadia, E. Tremblay, P. Vu, J. C. Cross and D. R. C. Natale (2017). "Sca-1 identifies a trophoblast population with multipotent potential in the mid-gestation mouse placenta." *Sci Rep* 7(1): 5575. <https://doi.org/10.1038/s41598-017-06008-2> PMID:28717241 PMCid:PMC5514127

Okae, H., H. Toh, T. Sato, H. Hiura, S. Takahashi, K. Shirane, Y. Kabayama, M. Suyama, H. Sasaki and T. Arima (2018). "Derivation of Human Trophoblast Stem Cells." *Cell Stem Cell* 22(1): 50-63 e56.

PrabhuDas, M., E. Bonney, K. Caron, S. Dey, A. Erlebacher, A. Fazleabas, S. Fisher, T. Golos, M. Matzuk, J. M. McCune, G. Mor, L. Schulz, M. Soares, T. Spencer, J. Strominger, S. S. Way and K. Yoshinaga (2015). "Immune mechanisms at the maternal-fetal interface: perspectives and challenges." *Nat Immunol* 16(4): 328-334. <https://doi.org/10.1038/ni.3131> PMID:25789673 PMCid:PMC5070970

Yang, Y., B. Liu, J. Xu, J. Wang, J. Wu, C. Shi, Y. Xu, J. Dong, C. Wang, W. Lai, J. Zhu, L. Xiong, D. Zhu, X. Li, W. Yang, T. Yamauchi, A. Sugawara, Z. Li, F. Sun, X. Li, C. Li, A. He, Y. Du, T. Wang, C. Zhao, H. Li, X. Chi, H. Zhang, Y. Liu, C. Li, S. Duo, M. Yin, H. Shen, J. C. I. Belmonte and H. Deng (2017). "Derivation of Pluripotent Stem Cells with In Vivo Embryonic and Extraembryonic Potency." *Cell* 169(2): 243-257 e225.

Young, B. C., R. J. Levine and S. A. Karumanchi (2010). "Pathogenesis of preeclampsia." *Annu Rev Pathol* 5: 173-192. <https://doi.org/10.1146/annurev-pathol-121808-102149> PMID:20078220