Inositol Trisphosphate Receptors in the Vascular Development

32

Keiko Uchida, Maki Nakazawa, Chihiro Yamagishi, Katsuhiko Mikoshiba, and Hiroyuki Yamagishi

Keywords
Intracellular calcium • Vascular development • Angiogenesis • Placenta

The placental circulation is crucial for the development of mammalian embryos [1]. The labyrinth layer in the placenta is created by extensive villous branching of the trophoblast and vascularization arising from the embryonic mesoderm. In the labyrinth, materials are exchanged between the maternal and embryonic circulation. Recently, we have found that inositol 1,4,5-trisphosphate (IP_3) receptors (IP_3Rs) may be required for the placental vascularization.

IP_3Rs are intracellular Ca^{2+} release channels that have three subtypes in mammals (IP_3R1, IP_3R2 and IP_3R3) [2]. We previously showed that IP_3R1 and IP_3R2 played an essential role in heart development from the analysis of mouse embryo double knockout for IP_3R1 and IP_3R2 [3]. A previous report on the

K. Uchida
Department of Pediatrics, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

Health Center, Keio University, 4-1-1 Hiyoshi, Kohoku-ku, Yokohama, Kanagawa 223-8521, Japan

M. Nakazawa • C. Yamagishi • H. Yamagishi (✉)
Department of Pediatrics, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
e-mail: hyamag@keio.jp

K. Mikoshiba
Laboratory for Developmental Neurobiology, RIKEN Brain Science Institute, Saitama 351-0198, Japan

Calcium Oscillation Project, International Cooperative Research Project and Solution-Oriented Research for Science and Technology, Japan Science and Technology Agency, Kawaguchi, Saitama 332-0012, Japan

T. Nakanishi et al. (eds.), *Etiology and Morphogenesis of Congenital Heart Disease*,
DOI 10.1007/978-4-431-54628-3_32

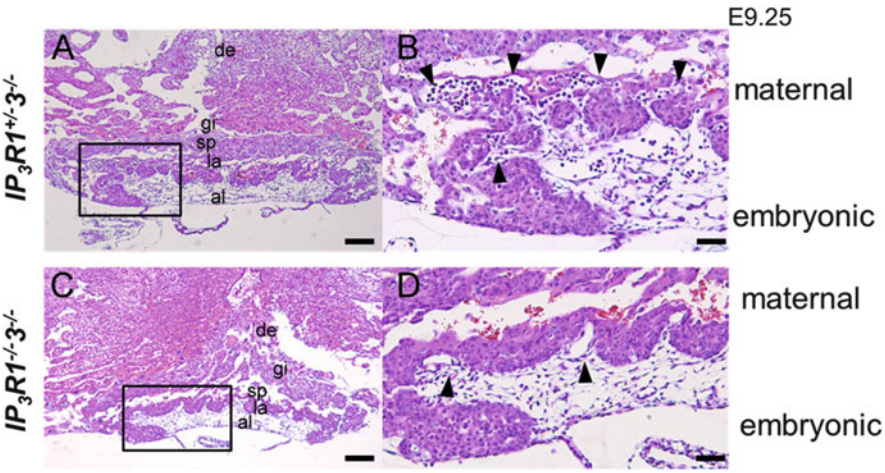

Fig. 32.1 Cross sections of E9.25 placentas from the $IP_3R1^{+/-}3^{-/-}$ (**a** and **b**) and $IP_3R1^{-/-}3^{-/-}$ (**c** and **d**) mice. (**b**) and (**d**) show higher-power fields of the *rectangular* areas of the labyrinth in (**a**) and (**c**), respectively. Embryonic vessels (*arrowheads*) fail to elongate to the maternal sinuses in the placenta of $IP_3R1^{-/-}3^{-/-}$ compared to that of $IP_3R1^{+/-}3^{-/-}$ (wild type). *al* allantois, *de* decidua, *gi* trophoblast giant cells, *la* labyrinth layer, *sp* spongiotrophoblast layer. Scale bars, 0.5 mm in (**a**) and (**c**) and 0.2 mm in (**b**) and (**d**)

requirement for phospholipase (PLC) δ1 and δ3 [4] that produce IP_3 for placentation led us to investigate the placental defects by deletion of any subtypes of IP_3Rs. Our preliminary result revealed that embryonic vasculature in the labyrinth was impaired in the placenta double knockout for IP_3R1 and IP_3R3 at E9.25 (Fig. 32.1). The detailed phenotype and the underlying mechanism how the intracellular Ca^{2+} signaling via IP_3Rs may be implicated in the development of extraembryonic vasculature are under investigation.

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan (to K.U. and H.Y.).

References

1. Rossant J, Cross JC. Placental development: lessons from mouse mutants. Nat Rev Genet. 2001;2:538–48.
2. Berridge MJ, Lipp P, Bootman MD. The versatility and universality of calcium signalling. Nat Rev Mol Cell Biol. 2000;1:11–21.
3. Uchida K, Aramaki M, Nakazawa M, Yamagishi C, Makino S, et al. Gene knock-outs of inositol 1,4,5-trisphosphate receptors types 1 and 2 result in perturbation of cardiogenesis. PLoS One. 2010;5:e12500.
4. Nakamura Y, Hamada Y, Fujiwara T, Enomoto H, Hiroe T, et al. Phospholipase C-delta1 and -delta3 are essential in the trophoblast for placental development. Mol Cell Biol. 2005;25:10979–88.