Science Advances: CNIC scientists identify the essential role of a gene in placental development

12/11/2021

A study published in Science Advances *shows that the gene GPR126, while not required for the development of the heart, plays an essential role in the formation of the placenta, the gestational organ that nourishes the fetus*

Scientists working with an experimental mouse model at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) have identified the essential role of the gene *GPR126* in the development of the placenta during pregnancy.

The results, published in *Science Advances*, show that GPR126 (adhesion G protein-coupled receptor 126) is essential for the development of a specific placental cell type that regulates the remodeling of the uterine vasculature. Cardiac defects in mouse *Gpr126* mutants are secondary to placental defects, reflecting the intimate relationship between the placenta and the fetal heart.

There is evidence that GPR126 may play a similar role in placental development in humans. The babies of women who carry mutations in GPR126 die during gestation or soon after birth, and 30% of these women develop preeclampsia. This pregnancy complication, which affects 5-8% of pregnancies in the general population, is characterized by high blood pressure that damages both mother and fetus and can result in fetal death.

Experiments in animal models have shown that GPR126 is required for the maturation of the peripheral nervous system (PNS), the formation of bone and cartilage, and the development of the inner ear. In humans, mutations in *GPR126* are associated with skeletal malformations and muscle cramping in the limbs.

The CNIC Intercellular Signaling in Cardiovascular Development and Disease group, led by Dr. José Luis de la Pompa, initially identified GPR126 as a gene regulated by the NOTCH signaling pathway (a highly conserved intercellular signaling system in animals) during heart development.

This suggested that GPR126 might influence the proliferation and differentiation of cardiomyocytes (heart muscle cells) in the developing heart.

Other groups had already proposed a requirement for GPR126 in heart development in mice and zebrafish, but research had not provided conclusive evidence to confirm this hypothesis.

In the new study published in *Science Advances*, the CNIC teamdemonstrate using genetic techniques that GPR126 is not necessary for heart development in the mouse but plays an essential role in the formation of the placenta, a process known as placentation

Explaining the results, Dr. de la Pompa said that “We observed that whole-body inactivation of GPR126 in mice caused thinning of the walls of the heart and resulted in embryonic death. However, when we inactivated the gene specifically in the heart, embryonic development was unaffected and heart function unaltered.”

The investigators also found that the lethal effect of whole-body GPR126 deletion “was not reversed by specific re-expression of GPR126 in the heart, indicating that embryonic death in the mutants was not due to a defect in cardiac development,” explained first author **Rebeca Torregrosa**.

Further studies in the zebrafish model confirmed that GPR126 “is not involved in heart development.

During embryonic development, GPR126 is expressed in giant trophoblast cells, a cell type specific to the placenta. “These cells,” indicated de la Pompa, “are vitally important for the implantation of the embryo and the maintenance of pregnancy.”

The research team demonstrated that GPR126 inactivation in the embryo is compatible with survival if the placenta retains at least one normal copy of the GPR126 gene. However, inactivation of the

gene in both the embryo and the placenta causes embryonic death

“One of the crucial steps in placental development is the remodeling of the maternal arteries. Known as the spiral arteries, these vessels increase their diameter to increase blood flow to the embryo. Defects in this process are associated with pregnancy complications such as preeclampsia, restricted fetal growth, and even miscarriage,” said José Luis de la Pompa.

The study shows that trophoblast GPR126 is necessary for the expression of specific proteases involved in spiral artery remodeling, which is essential for the viability of the fetus.

Based on these results, the investigators herald mice lacking GPR126 as an experimental model for studying spiral artery remodeling and preeclampsia. This animal model, moreover, has possible clinical applications in preimplantation genetic diagnosis.

The study was funded by the CIBER CV cardiovascular research network CIBER CV (PID2019-104776RB-I00, CB16 / 11/00399), TERCL (RD16 / 0011/0021) del Ministerio de Ciencia de España, Innovación y Universidades (MCIU), BBVA Foundation, ” La Caixa” Foundation, EMBO fellowship, Boehringer Ingelheim Fonds, y el Programa de Atracción de Talento de la Comunidad de Madrid (Ref.2016T1 / BMD1540).

- *Torregrosa-Carrión R., Piñeiro-Sabarís R...,de la Pompa J. Adhesion G protein-coupled receptor Gpr126/Adgrg6 is essential for placental development; Science Advances DOI: 10.1126/sciadv.abj5445*

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