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Research Highlight
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Placental defects are involved in most gene mutations that cause embryonic and fetal death

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The placenta represents a vital organ essential for successful reproduction of all viviparous mammals. Our knowledge on the mechanisms of placental development remains rather limited although its necessity for health of the fetus and the mother has long been recognized. As the interface between fetal and maternal environments in utero, the placenta is responsible for the exchange of gases, nutrients and waste products between the mother and the fetus. It also functions as a temporary endocrine organ during pregnancy by producing hormones (e.g., estradiol and progesterone) and paracrine factors (e.g., various cytokines, growth factors) to support and modulate maternal adaptations to pregnancy, and to protect the fetus from maternal immune attack. Disrupted placental development leads to adverse pregnancy outcomes and even fetal lethality, as documented by numerous human and animal studies [1]. In humans, common pregnancy-related diseases, e.g. preeclampsia, recurrent spontaneous abortion, preterm birth, and fetal growth restriction, have been associated with placental defects. However, we know very little about the working mechanisms of this important organ during embryonic and fetal development. By far, the placenta is understudied and consequently one of the least understood organs. Only a limited number of causative factors has been identified so far, which are either derived from the placenta or capable of influencing placentation. For instance, excessive production of soluble VEGF receptor-1 (sFlt-1) coupled with downregulation of placental growth factor in the placenta has been widely used as etiological biomarker for preeclampsia [2]. Studies using gene knockout mice have revealed several signaling pathways (e.g., HGF/c-Met, Wnt/β-catenin, VEGF, and Notch) and transcription factors (e.g., Gcm1 and Mash2) that are critical for normal placental development and fetal fate [3]. Despite the progress made, the complete molecular frameworks that govern placental development and thus, pregnancy outcomes, remain to be defined.

In a recent issue of *Nature*, Hemberger and colleagues report a groundbreaking study, which, for the first time, makes a systematic attempt to reveal the extent to which genes that cause fetal developmental defects and embryonic lethality are linked to placental dysfunctions [4]. This phenotyping program is termed "Deciphering the Mechanisms of Developmental Disorders" (DMDD; http://dmdd.org.uk), with all data deposited in a publically accessible database, which will become a rich resource to the research community. The insights provided from this DMDD program highlight that two-thirds of all gene mutations that cause embryonic lethality exhibit placental phenotypes. This number is far higher than the 10% described in mouse knockout databases, highlighting the hugely underestimated extent to which genes that are critical for embryo development also cause placental defects.

As indicated by the authors, traditionally most studies of mouse mutants including large-scale knockout screens have paid much more attention to the analysis of embryonic/fetal phenotypes, while leaving potential placental defects neglected. Previous tetraploid complementation and conditional knockout studies have shown, however, that a compromised placenta can be causative of fetal lethality [5, 6]. While it remains to be seen in how many mutants analyzed in this current study the placenta is indeed the cause of embryonic lethality, the authors' efforts to follow up three mutant lines in conditional knockouts, leaving gene function in the placenta intact, proves that a considerable number of embryonic defects may indeed result from a defective placenta.

The most appealing results of this study are the large-scale phenotyping analyses of >100 mutant mouse lines, for which both the embryo and placenta were assessed in-depth for morphological defects. By using the genes that cause placental defects at either E9.5 or E14.5 of development for network analyses, the authors identified specific molecular pathways that may be critical for certain cell differentiation events during the functional development of the placenta. The genes that affect placentation at E9.5 form functional gene clusters centered around *L3mbtl2*, *Bap1*, and *Arhgef7*, and their mutations most frequently lead to defects in the invagination of allantoic blood vessels into the chorionic ectoderm. Such serious deficiencies interfere with the establishment of the feto-maternal exchange interface, which is required at mid-gestation to allow development to progress. Prevalent phenotypes of gene mutations that caused placental abnormalities at E14.5 often entailed insufficiencies in the growth and intricate organization of the fetal and maternal blood conduits within the labyrinth layer, and the responsible

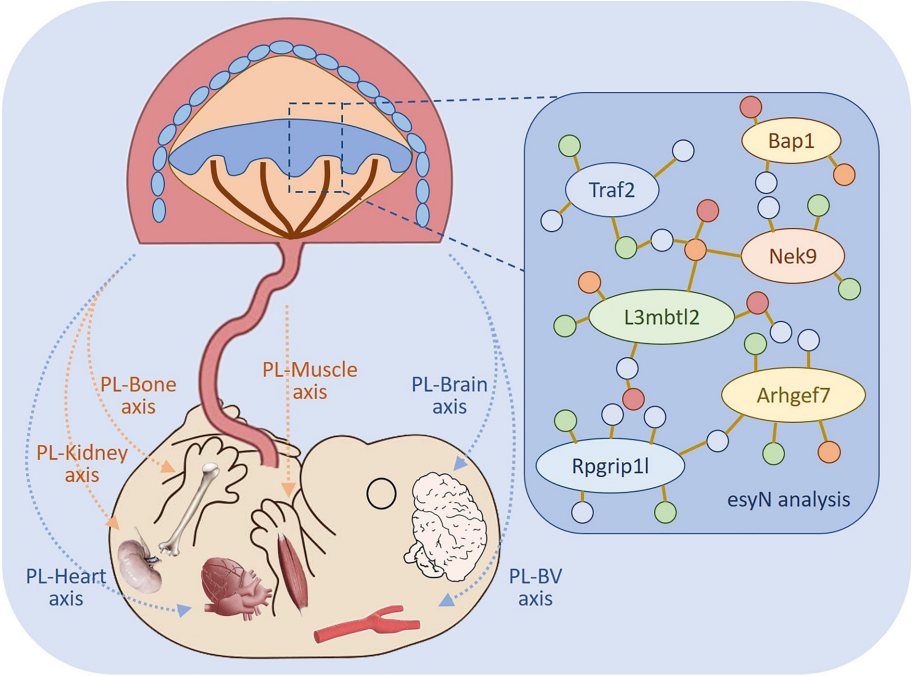

Figure 1. Placental development impacts embryonic health. Blue arrow lines indicate the placenta–fetal organ axes revealed in the highlighted paper, whereas red arrow lines show some other hypothesized axes based on data mining. PL, placenta; BV, blood vessels.

molecular nodes involves *Traf2*, *Nek9,* and *Rpgrip1l*. Placental and fetal development is a dynamic and coordinated process. The ample data reported in this study will allow for more discoveries of the molecular cascades that govern cellular events at different stages of gestation. Although the data are derived from the mouse model, considering the functional comparability between human and mouse placenta, this study is of great value in understanding the pathogenesis of complex pregnancy-related diseases in humans.

In addition to advancing knowledge of gene function in the placenta, the DMDD phenotyping program also incorporates a detailed analysis of the embryo itself. By comparing gene knockout lines that cause a placental phenotype with those that do not, the authors show that specific embryonic phenotypes are enriched in mutants with placental defects. Among the most prevalent fetal phenotypes tightly associated with placental defects are abnormalities in the fetal heart, brain and vascular system, a coassociation that we here term the "placenta–heart/brain/vascular system axis" (see Figure 1). In particular, common anomalies were observed in forebrain development, heart chamber and septum morphology, subcutaneous edema, and overall artery or vein topology [4]. Epidemiological studies have demonstrated that pregnancy complications, e.g., preeclampsia, preterm birth and fetal growth restriction, are predictive of high risk of cardiovascular diseases in the offspring [7]; however, the underlying mechanism remains unclear. Besides the three genes mentioned by the authors for their possible connection with human placental disorders (*TRAF2*, *PSPH*, and *BAP1-ASXL3*), some other genes among the list of mouse mutants with placental defects, such as *Rpgrip1l*, *Nek9*, and *Slc25a20*, have been reported to correlate with renal and skeletal diseases and myopathy in humans [8, 9]. This study provides strong evidence supporting the notion that placental defects are linked with, and possibly constitute—at least in some instances—a direct cause of disrupted fetal heart and vascular development, leading to severe birth defects or long-term cardiovascular problems in the offspring. Therefore, it is plausible to hypothesize that the axis may exist between the placenta and a wide variety of embryonic organs. If so, in utero interference by targeting the placenta may be an efficient and safe means to correct abnormalities in the fetus.

In summary, this study underscores the importance of the placenta during embryonic and fetal development. In humans, gene networks that bridge placenta defects and adverse pregnancy outcomes and fetal health remain to be systematically elucidated. In the future, a combination of genomic analyses and high-resolution imaging may help to more precisely evaluate placental development, and the information may be used to monitor fetal health or predict long-term health of the offspring. These future efforts will not only deepen our understanding of the enigmatic placenta, but also help improve health of both women and their offspring.

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