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Only humans have human placentas: molecular differences between mice and humans

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ABSTRACT

The placenta is one of the organs with the highest evolutionary diversity among animal species. In consequence, an animal model that reflects human placentation exactly does not exist. However, the mouse is the most frequently used animal model for placenta and pregnancy research. It possesses a hemochorial placenta, which is similar, but also different from the human placenta. The question whether the similarities are sufficient for the achievement of useful results with regard to human pregnancy was debated recently at the 11th Congress of the European Society for Reproductive Immunology (Budapest, Hungary). Here, we discuss the molecular features of the human placenta that are restricted to primates or even to humans. Many of the primate-specific genetic novelties, e.g., the large microRNA cluster on chromosome 19, have been detected during the last 10–15 years and could not be referred to in earlier discussions. Now, in the light of recent findings and a better understanding of interspecies differences, we conclude that the mouse model is often overvalued. Owing to the increasing number of known human-specific factors in human placentation we consider that many aspects of human placentation can only be understood on the basis of experiments on human cells and tissues in combination with data collections from human subject studies.

1. Introduction

The mouse is the most frequently used animal model. Originally, the main reasons for this choice were not the similarity to humans, but the fact that mice are small, have a large litter size and short generation times, all features that are very practical for laboratory work. However, in recent years, the value of animal models in general and the mouse model in particular has been questioned more and more as genomic data on the one hand and experimental outcomes on the other hand have revealed marked differences between humans and all other mammals. It is considered that these differences are at least partly responsible for the slow advances in the treatment of serious diseases or the failure to predict serious adverse effects as in cases such as the disastrous clinical phase I trial of TGN1412 (Stebbings et al., 2007). Indeed, the fact that only a very small portion of the drugs that are successful in preclinical animal models enter the market (Hartung, 2013) clearly indicates that the failure of animal models (but also of the applied in vitro models) is rather systemic than restricted to single events. This is supported by a variety of publications on, e.g., inflammatory diseases (Seok et al., 2013), multiple sclerosis (Raddatz et al., 2014), diabetes (Chandrasekera and Pippin, 2014), Alzheimer's disease (Cavanaugh et al., 2014),

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Table 1
While the human placenta shows characteristics that developed in the course of primate evolution (left) the mouse has traits that are absent from primates (right).

Humans and (some) other primates	Mouse
- Chorioallantoic placenta	- Chorioallantoic placenta and yolk sac placenta
- Fetal placenta with intervillous space	- Placental labyrinth
- Monochorial	- Trichorial
- Trophoblast invasion into the inner third of the myometrium	- Trophoblast invasion restricted to the decidua
- (Hyperglycosylated) chorionic gonadotropin	-Absent in mice
- LHCGR with exon 6a	- Absent in mice
- Gene clusters for placental lactogens/growth hormones and placental galectins	- Gene clusters for prolactin-related genes and cathepsins
- Estrogen synthesis in placenta	- Absent in mice
- KIRs on natural killer cells	- Ly49 expression on natural killer cells
- HLA-C	- H2-K
- HLA-G, HLA-E	- Absence of nonclassical MHC class I molecules on trophoblast surface
- Glycodelin A	- Absent in mice
- miRNA cluster on chromosome 19	- *Sfmbt2 miRNA* cluster on chromosome 2
- Syncytin-1 and -2; suppressyn	- Syncytin-A and -B

Table 2
According to the present knowledge, the human placenta is characterized by a range of human-specific molecular novelties that cannot be found in any other mammals.

Human-specific features of the placenta
- KIR B haplotype
- Siglec-6 expression in placenta
- IMUP-2
- Several miRNAs (e.g., hsa-mir-941); miRNA targets
- Absence of Neu5Gc synthesis
- sFlt1-14

cancer (Ellis and Fidler, 2010), and atherosclerosis (Cullen et al., 2003). Furthermore, Hartung has summarized that the predictability of animal experiments in toxicology of two species is not better than 53–60%, which is close to pure chance (Hartung, 2009). Generally, it is interesting to note that problems with the translation of animal experiments are not restricted to evolutionary distant species like rodent models, but that striking differences exist even between humans and their closest relatives, the chimpanzees (Varki and Altheide, 2005; Bailey, 2011).

Bearing in mind such differences and being aware of the fact that the placenta is an organ with outstanding evolutionary diversity the question arises whether animal models of placentation are rather constructive or confusing with regard to the human biology, especially in the case of the most frequently used mouse model. Here, we aim to highlight several aspects of species differences between these two organisms, indicating that the species mouse should be regarded very critically as a model for human placentation and pregnancy (Tables 1 and 2).

2. Interspecies differences in placental anatomy

In contrast to other potential animal models such as dogs (endotheliochorial) and pigs (epitheliochorial) the mouse possesses a hemochorial placenta, which means that the trophoblast layer is in direct contact with the maternal blood and not separated by endothelium and/or epithelium. Thus, the chorioallantoic placentas of mice belong to the same group as human placentas. However, on further study it becomes obvious that the similarity is rather gross as striking differences can be found when comparing the anatomy, the cell types, and the molecular biology.

Before approaching these differences, probably the most impressive divergence between mouse and human is the fact that mice, in addition to the chorioallantoic placenta, have a choriovitelline placenta – the inverted yolk sac placenta – which becomes active early in pregnancy and persists until term. This kind of placenta, which is typical for rodents, is completely absent from humans, but plays an irreplaceable role in rodent pregnancy with failures leading to embryo malformations (Beckman et al., 1990). The existence of a second placental structure is accompanied by several problems with regard to the value of mouse experiments. The development of the inverted yolk sac placenta can be affected by chemicals and pharmaceuticals (Beckman et al., 1990; Haghighi Poodeh et al., 2012). Principally, with regard to humans, this may result in the possibility of false-positive observations of adverse effects (Holson et al., 2005), one of the central problems in toxicity testing. Further, human placental transfer cannot be mimicked well in mouse models as substances may pass the yolk sac placenta. It is interesting that plutonium is trapped effectively in the yolk sac placenta of mice and rats (Kubota et al., 1993), which may result in the maldevelopment of the yolk sac placenta (National Research Council (U.S.). Committee on the Biological Effects of Ionizing Radiations, et al., 1988). Further, plutonium is discussed as being a potential factor for an increased risk of childhood leukemia (Morgan et al., 1991), leading to the assumption that yolk sac accumulation may have a protective effect on the fetus as the access of plutonium to the fetus should be much more limited. Indeed, this is supported by data showing that whole-body fetal:maternal concentration ratios (C_F:C_M) for plutonium in a comparable state of late pregnancy is 1.3 in baboons, like humans, a species without a yolk sac placenta, while it is 0.06 for rats (Paquet et al., 1998).

Another possible implication is mentioned by Nau (2001): in rodents the chorioallantoic placenta is preceded by the functional yolk sac placenta. Thus, in comparison to rodents the chorioallantoic placenta in primates develops during an earlier period when the embryo is less developed and more sensitive to teratogenic effects. Therefore, even