Minireview

The Role of the Placenta in Fetal Exposure to Xenobiotics: Importance of Membrane Transporters and Human Models for Transfer Studies

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ABSTRACT:
The placenta is a key organ in fetal growth and development because it controls maternal-to-fetal exchanges of nutrients and hormones. It also interferes with drug delivery to the fetus by expressing active membrane transporters and xenobiotic metabolism enzymes. Developing strategies to understand the role of the placenta in drug delivery is a challenge in toxicology. Despite common physiological functions, the placentas of different species are heterogeneous in their morphology and in their expression of membrane transporters and metabolizing proteins. These characteristics raise the difficulty of obtaining a good representative model of human placental transfer. To date, different in vitro, in vivo, and ex vivo tools have been used to elucidate transport and metabolism processes in the human placenta. This study recapitulates the typical features of human placenta and then presents the placental enzymes of xenobiotic metabolism, ATP-binding cassette transporters, solute carrier transporters, and their role in fetal exposure to xenobiotics. The study also compares the characteristics of different models of human placenta, in terms of membrane localization of transporters, and the expression of xenobiotic metabolism enzymes. The use of these models for toxicological studies, in particular xenobiotic transfer, is described, and the advantages and limits of each model are summarized.

Introduction

The placenta is a key organ for the growth and development of the embryo and fetus during pregnancy: this semipermeable barrier separates the mother and the fetus and regulates the exchange of nutrients, gases, waste, and endogenous and foreign molecules between maternal and fetal circulations. It has traditionally been considered as a highly permeable organ for a large variety of substances with diverse molecular structures that are readily able to cross it from the maternal blood to reach the fetus. Indeed, proof of fetal exposure to maternal intake occurred for the first time with the thalidomide disaster in 1957 to 1961. As a result, experts recommend the limited use of drugs during pregnancy, if possible.

The human placenta barrier consists of a single limiting layer of multinuclear cells, which are known as syncytiotrophoblasts (Enders and Blankenship, 1999). A microvillus brush border membrane, in direct contact with maternal blood, constitutes the maternal-facing plasma membrane of the syncytium. On the opposite side, the basal membrane faces the fetal circulation and lacks microvillar projections. Both sides of the syncytium are not only structurally distinct, but they also differ in the localization of transporters, enzymes, and hormone receptors. The current knowledge about the existence of different systems, including plasma membrane carriers, biotransforming enzymes, and export pumps, that determine the selectivity and efficacy of the so-called placental barrier is underlined. A good understanding of the molecular bases of these processes and their regulation is crucial for predicting the risk of fetal exposure to active agents.

In addition to drug exposure, which can be voluntarily limited during pregnancy, fetal exposure to food contaminants is characterized by chronic exposure to low doses. Very little information is available on fetal exposure to these pollutants and their long-term effects. Drug transporters are involved in the regulation of the chemical environment of the fetus by selectively transporting and removing toxic substrates. Thus, placental epithelia expressing xenobiotic metabolism enzymes and transport proteins are very helpful models for the in vitro study of quantitative and qualitative transfers of molecules to the fetus.

ABBREVIATIONS: P450, cytochrome P450; ABC, ATP-binding cassette; MDR1, ABCB1, multidrug resistance-associated proteins; P-gp, P-glycoprotein; PSC833, 6-[(2S,4R,6R)-4-methyl-2-(methylamino)-3-oxo-6-octenoic] cyclosporine D; GG918, N-[4-[2-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolinyl)-ethyl]-phenyl]-9,10-dihydro-5-methoxy-9-oxo-4-acridine carboxamine; MRPs, ABCCs, multidrug resistance proteins; BCRP, ABCG2, breast cancer resistance proteins; PhIP, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine; SLC, solute carrier; OATP, organic anion-transporting polypeptide; OAT, organic anion transporter; OCT, organic cation transporter; OCTN, organic cation/carnitine transporter; SERT, serotonin transporter; NET, norepinephrine transporter; MCT, monocarboxylate transporter; ENT, equilibrative nucleoside transporter; FRα, folate receptor alpha; RFC-1, reduced folate carrier 1; PCFT/HCP1, proton-coupled folate transporter/heme carrier protein 1; hCG, human chorionic gonadotropin; IFN, interferon; IL, interleukin; ASCt, amino acid transporter; SNP, single nucleotide polymorphism.
Different experimental trophoblast systems are available, including immortalized cell lines, which are derived from normal and malignant tissues. In this review, we present a synthesis on xenobiotic metabolism enzymes and transporters in the placenta and update the different experimental models potentially available for the study of the barrier function.

Physiological Function of the Human Placental Barrier

Similar to other primate species, the human placenta is hemochorial and characterized by direct contact between maternal blood and trophoblast (Fig. 1a). The human placenta is divided into functional vascular units called cotyledons. Within the cotyledon, the villus tree contains a barrier that separates maternal circulation from fetal circulation. The layer of tissue that separates maternal and fetal circulation is composed of the endothelium of fetal capillaries and the trophoblast, which contains the villus strom, the cytotrophoblasts, and the syncytiotrophoblast. The thickness of the syncytiotrophoblast layer decreases during gestation, the cytotrophoblast becomes discontinuous, and exchange processes between mother and fetus are facilitated (van der Aa et al., 1998) (Fig. 1b).

The major function of the placenta is the transfer of nutrients that support embryonic and fetal growth and development. During early gestation, the placenta mediates the implantation of the embryo in the uterus and produces hormones that prevent the end of the ovarian cycle. The luteinizing hormone and the human chorionic gonadotropin have a stimulating action on estrogen and progesterone synthesis during the luteal phase of the menstrual cycle. The luteinizing hormone and the human chorionic gonadotropin are produced by the placenta (Pasqualini and Kincl, 1985). After implantation, the placenta mediates the implantation of the embryo in the uterus and produces hormones that prevent the end of the ovarian cycle. The luteinizing hormone and the human chorionic gonadotropin have a stimulating action on estrogen and progesterone synthesis during the luteal phase of the menstrual cycle. 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CYP19 and CYP11A are the major isoforms expressed (mRNA quantification) (Nishimura et al., 2003). Human placenta contains a few forms of phase II enzymes: glutathione S-transferase α and π (Pacifici and Rane, 1981; Pasanen et al., 1997), epoxide hydrolase (Pacifici and Rane, 1983), N-acetyltransferase (Dereiwany et al., 1994), and sulfotransferases isoforms such as SULT1A1 and

![Diagram of human placental structure](image-url)
deshydrogenase enzymes have been reported (Table 1). Data on enzymes of xenobiotic metabolism which are expressed (Collier et al., 2002a,b). UDP-Glucuronyltransferase isoforms, such as UGT1A and UGT2B, are also expressed (Collier et al., 2002a,b). Data on enzymes of xenobiotic metabolism contents in placenta cell lines are very scarce compared to those for the whole organ: only a few P450s, including CYP19, and hydroxysteroid dehydrogenase type 1 (Mitra and Audus, 2009). SULT1A3 (Mitra and Audus, 2009). In 1998, the report of carrier-mediated transport of xenobiotics in the placenta stressed the role of ATP-binding cassette (ABC) transporters in this organ (Lankas et al., 1998). Depending on the localization of these transporters in the apical (maternal facing brush border membrane) and basal (fetal facing basal membrane) membrane of the syncytiotrophoblast, the substrates are preferentially transported either in maternal circulation or in fetal circulation (Unadkat et al., 2004). Placental xenobiotic transporters and their polarized distribution are summarized in Table 2.

Membrane Transport in Placenta

Transplacental Transfer of Xenobiotics. The transfer of molecules between maternal and fetal circulation occurs across the endothelial-syncytiotrophoblast membrane of the placenta. Drug permeation can be influenced by numerous factors: drug properties (degree of ionization, lipophilicity, protein binding, molecular weight); placental characteristics (blood flow, concentration gradient of the drug across the barrier, pH gradient, thinning and aging barrier with advancement of pregnancy, increasing surface area as pregnancy progresses, developing metabolism, protein gradients); and maternal and fetal factors (fetal growth and development, fetal metabolism, fetal tissue binding, maternal metabolism, maternal health condition) (Poulsen et al., 1998). Most of the drugs crossing the human placenta diffuse passively. In this case, placental blood flow, pH of maternal and fetal blood, physicochemical characteristics of the compounds, and protein binding determine a drug’s ability to cross placental membranes (Pacifici and Nottoli, 1995; Audus, 1999). Facilitated diffusion, phagocytosis, and pinocytosis are less important routes of placental drug transfer (Syme et al., 2004).

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ABC Transporters

P-Glycoprotein (MDR1, ABCB1). The placental barrier had been commonly considered as a permeable barrier, until a study was published by Lankas et al. (1998). These authors stressed the role of P-glycoprotein (P-gp) in the mouse placenta by exposing pregnant dams, which contained a spontaneous mutation in the mdr1 gene, to the teratogenic isomer of avermectin [1.5 mg/(kg day)], which is a substrate of P-gp. They demonstrated that the degree of chemical exposure to fetuses within each litter was inversely related to the expression of placental P-gp, linking the fetal genotype to pharmacokinetic changes and subsequently to developmental toxicity.

Other studies confirmed the involvement of P-gp in the limited fetal penetration of various potentially harmful or therapeutic compounds such as digoxin, saquinavir, paclitaxel (study performed in P-gp-deficient mice) (Smitt et al., 1999), and indinavir (study using an in vitro

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dose of P-gp substrate digoxin, saquinavir, and paclitaxel to pregnant fetus, compared with the wild-type H11001/H11001 (1b). These results were confirmed by Evseenko et al. (2006a), who identified MDR3 protein in the basolateral membrane of the syncytiotrophoblast layer of the term placenta and suggested that MDR3 mediated the vectorial transport of substrates toward the fetus. MDR3 functions as a lipid translocator and may also interact with pharmaceutical drugs (Kimura et al., 2007). Although an overexpression of MDR3 was reported in resistant tumor cells (Scheffer et al., 2000), the role of MDR3 in multidrug resistance is probably minor and remains to be confirmed.

Multidrug Resistance-Associated Proteins. The human term placenta expresses at least three members of the MRP family: MRPs, MRPs, and MRP3 (St-Pierre et al., 2000). The localization of MRPs has been studied using human placental brush-border, basal membrane vesicles and immunohistochemical studies, but the results are controversial, because both apical (St-Pierre et al., 2000) and basal (Nagashige et al., 2003) localization have been reported. MRPs were clearly detected by both immunofluorescence and Western blotting in the apical membranes of syncytiotrophoblasts, whereas immunoblotting suggested an apical localization facing the maternal blood of the term placenta (St-Pierre et al., 2000). MRPs mRNA have been identified in placental cell lines: MRP1 and MRP2 transcripts were found in the human choriocarcinoma cell line BeWo (Pascolo et al., 2000; Prouillac et al., 2009).

The mRNA expression of MDR3 (MDR1 homolog, ABCB4) has also been reported in human term and preterm placenta by Patel et al. (2003). These results were confirmed by Evseenko et al. (2006a), who identified MDR3 protein in the basolateral membrane of the syncytiotrophoblast layer of the term placenta and suggested that MDR3 mediated the vectorial transport of substrates toward the fetus. MDR3 functions as a lipid translocator and may also interact with pharmaceutical drugs (Kimura et al., 2007). Although an overexpression of MDR3 was reported in resistant tumor cells (Scheffer et al., 2000), the role of MDR3 in multidrug resistance is probably minor and remains to be confirmed.

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Steroid sulfates that allow estrogen synthesis in the placenta, it is also a multispecific xenobiotic transporter that could interact with environmental toxins and drugs (You, 2004a,b) and contribute to fetal exposure to xenobiotics.

**Organic Cation Transporters.** Different organic cation transporters have been identified in the human placenta. The organic cation/carnitine transporter 1 (OCT1), a member of a subfamily of OCTs (SLC22A subfamily), is expressed on the apical side of human syncytiotrophoblasts (Tamai et al., 1997; Ganapathy et al., 2005). OCTN2 is also present on the maternal side (microvillous membrane) of trophoblast cells, as shown by Lahjojii et al. (2004). OCTN2 transports t-carnitine in a Na+-dependent manner, from maternal circulation to fetal circulation. It can also mediate the transport of drugs such as antidepressants, amphetamines, and β-lactam antibiotics (Grube et al., 2005). OCT3 is a Na+- and Cl−-independent monoamine transporter that is mostly found in the placenta (Kekuda et al., 1998). OCT3 transcript and protein have been detected at the basal membrane of human trophoblast cells (Sata et al., 2005). Because it shows a high affinity for monoamines (serotonin, dopamine, norepinephrine, and histamine), human OCT3 is considered to be an extraneuronal monoamine transporter. However, antidepressants (desipramine, imipramine, amphetamines) could also interact with OCT3.

**Monoamine Transporters.** The serotonin transporter (SERT) and the norepinephrin transporter (NET) have been identified in the placenta at the maternal facing membrane (Prasad et al., 1996; Bzoskie et al., 1997). Both SERT and NET proteins are functionally active in the human placenta at term. Because these transporters critically regulate extracellular monoamine concentrations, they could play a role in maintaining homeostasis in amniotic fluid and fetal circulation (Prasad et al., 1994a): they clear the maternal blood of excessive amounts of catecholamines and serotonin, preventing preeclampsia (Bottalico et al., 2004). In addition, the monoamine oxidases A, which allow the intracellular degradation of monoamines after uptake from the extracellular space, are less expressed and less active in placentas from preeclamptic pregnancies (Kaaja et al., 1999; Carrasco et al., 2000; Sivasubramaniam et al., 2002). Monoamine transporters have been involved in the adverse effects of cocaine and amphetamines, because they are cellular targets for these abusable drugs that block catecholamine transport (Ramamoorthy et al., 1995; Prasad et al., 1996; Bzoskie et al., 1997).

**Monocarboxylate Transporters.** There are several isoforms of monocarboxylate transporters (MCT1, MCT3, MCT4, MCT5, MCT7, MCT8) (Price et al., 1998; Settle et al., 2004) and dicarboxylate transporters (NaDC3) (Wang et al., 2000) in the placenta. These proton-coupled transporters are essential for the transport of lactate, ketone bodies, and other monocarboxylates through the plasma membrane. They may contribute to the net transport of lactate through the placental barrier (Nagai et al., 2010). MCT8 could be involved in the transport of thyroid hormones and implicated in the development of trophoblast cells and the fetus (Chan et al., 2006). Other substrates are benzoic acid, acetic acid, acetylsalicylic acid, and antibiotic cefdinir (Utoguchi et al., 1999).

**Equiribative Nucleoside Transporters.** Both Na+-independent equiribative nucleoside transporters, ENT1 and ENT2, are expressed in the placenta (Barros et al., 1995). Physiological substrates of these transporters are purine and pyrimidine nucleosides, but a number of anticancer nucleoside analogs are also substrates (Griffiths et al., 1997).

**Folates Transporters.** Because folates are essential nutrients for cell division and growth, folates’ deficiencies by insufficient dietary intake could impair fetal development. In addition to their involve-
ment in folate transport, these transporters could interact with a variety of antifolates used in the treatment of cancer and immune disorders.

Folate receptor alpha (FRα), localized on the apical side of human placental villi, could be involved in folate uptake from maternal blood to the placenta (Prasad et al., 1994b; Yasuda et al., 2008). Reduced folate carrier (RFC-1; SLC19A1) is distributed to both the microvillous plasma membrane of the syncytiotrophoblast and the basal syncytiotrophoblast in term placenta (Yasuda et al., 2008; Solanky et al., 2010), and it mediates bidirectional reduced folate transport. More recently, a heme carrier protein 1 (PCFT/HCP1, SLC46A1) implicated in folate transport has been characterized in the apical side of the trophoblast.

Most studies on the placental expression of transporters have been performed in various models that represented different stages of gestation. Therefore, it is very difficult to compare the levels of expression from one stage of gestation to another. Data on the expression of transporters throughout gestation are necessary to understand their importance in fetal development. Indeed, the expression of numerous transporters varies during pregnancy.

Variation of Transporter Expression during Pregnancy

The continuous development of placenta defines different stages of pregnancy and results in modifications of permeability, which potentially lead to modulation of fetal exposure. Among ABC transporters, ABCG2, ABCB1, ABCB3, and ABCC1 have been shown to vary during pregnancy.

ABCG2. Different in vivo studies have shown a clear variation in ABCG2 expression as gestation progresses. Indeed, BCRP protein expression and mRNA increased 2-fold in a group of preterm placentas (28 ± 1 week of pregnancy, 15 placentas), compared with term placentas (39 ± 2 week of pregnancy, 29 placentas) (Meyer zu Schwabedissen et al., 2006). On the contrary, Yeoboah et al. (2006) examined BCRP in placental tissues at week 6 to 41 of pregnancy and reported an increase in protein expression at term, although mRNA levels did not change as gestation progressed. In the rat placenta, a decrease in the expression of Bcrp1 (mRNA and protein) from the mid-stage to the end of gestation was observed (Yasuda et al., 2005). Bcrp1 mRNA expression increased 3-fold on the 15th day of gestation compared with the 21st day (Cygalova et al., 2008). In agreement with the latter study, two recent studies on mouse placenta reported peaked Bcrp1 levels on the 15th gestation day (Wang et al., 2006) and a gestation-dependent decrease in the mRNA expression of Bcrp1 from the 9th to the 18th day of gestation (Kalabis et al., 2007).

ABCB1, ABCB3. The mean expression of P-gp measured by Western blotting analysis in early (13–14 gestation week) compared with late (full-term) placentas was found to be 2-fold higher (Gil et al., 2005; Sun et al., 2005). In agreement with this finding, Mathias et al. (2005) demonstrated that the P-gp expression protein decreased dramatically as pregnancy proceeded and was lowest at term. On the other hand, Novotna et al. (2004) showed increasing expression of P-gp in rat syncytiotrophoblasts from the 11th to the 18th day of pregnancy. This result was in agreement with a possible role in fetal protection soon after the establishment of chorioallantoic placenta and until the end of pregnancy. Unlike human MDR1, human MDR3 was more abundantly expressed in the last stage of gestation (Patel et al., 2003).

Existing data strongly suggest that ABCG2 and ABCB1 play an important role in protecting the fetus against the potential toxicity of drugs, xenobiotics, and metabolites. The decrease in ABCG2 and ABCB1 at the end of gestation could be related to higher fetal susceptibility to xenobiotic toxicity in the last part of gestation and higher fetal protection against xenobiotics early in pregnancy. Indeed, the fetus is most vulnerable to xenobiotic toxicity during organogenesis.

ABCC1. In a study using placental samples (cytotrophoblasts and endothelial cells), MRPI expression was increased 4-fold in the third trimester, compared with the first trimester (Pascolo et al., 2003). MRPI was also increased 20-fold in polarized BeWo cells, compared with nonpolarized cells.

OATPs. Among SLC transporters, OATP1A2 and OATP3A1 were down-regulated between the first and third trimester of pregnancy (Patel et al., 2003).

The discrepancies observed in rats, mice, and humans suggested different mechanisms in the regulation of transporter expression among these species. However, the molecular mechanisms underlying the modulation of placental ABC and SLC transporters by pregnancy have not been elucidated yet.

Folate Transporters. An increase in the expression levels of FRα, RFC, and PCFT and the progress of gestation in rat placenta have been shown and could play an important role in the response to increased need by placenta and fetus for folate during development (Yasuda et al., 2008).

Due to obvious ethical reasons, studies of fetal risk from maternal exposure to chemicals and pharmaceuticals are not performed in humans. In addition to in vivo/ex vivo models, cell lines have been developed to provide important knowledge on the transplacental transfer in humans of new chemical substances and on environmental exposures to hazardous compounds. The use of nondifferentiated models, such as choriocarcinoma cell lines, is also an alternative in the study of the expression of transporters during early stages of gestation.

The Use of Cell Lines as Placental Barrier Models

The properties and main uses of these cell lines are summarized in Table 3.

Human Choriocarcinoma Cell Lines

BeWo Cell Line. The BeWo cell line (Patillo and Gey, 1968), developed from a malignant gestational choriocarcinoma of the fetal placenta, displays morphological and biochemical enzymes of trophoblasts, which show hormonal secretion properties (hCG, progesterone, placental lactogen) (Patillo et al., 1979; Nickel and Cattini, 1991) and cytokine expression [IFNα, IFNβ, IL10 (Bennett et al., 1996), IL6 and IL8 (Fujisawa et al., 2000), and IL4 (Sacks et al., 2001)].

The BeWo cell line is widely used as a model system to study trophoblast differentiation (Hussa et al., 1974; Vogt et al., 1997; Xu et al., 1999; Rao et al., 2003; Rote, 2005), placental metabolism, and nutrient and drug distribution across the placental barrier (van der Ende et al., 1989; Furesz et al., 1993; Moe et al., 1994; Prasad et al., 1996; Eaton and Sooranna, 1998; Way et al., 1998; Ellinger et al., 1999; Ushigome et al., 2000; Shah et al., 1999; Takahashi et al., 2001; Vardhana and Illsley, 2002; Schmid et al., 2003). BeWo cells form a confluent polarized monolayer on a permeable support, as shown by the development of a transepithelial electric resistance and a high density of microvilli on the apical surface of the monolayer (Liu et al., 1997). The b24 and b30 BeWo clones (developed by Dr. Alan Schwartz, Washington University School of Medicine, St. Louis, MO) have shown better monolayer-forming ability than the original BeWo clone available from the American Type Culture Collection (Manassas, VA) (Bode et al., 2006). This finding contradicts studies by Parry et al. (2006) and Mark and Waddell (2006) who used the BeWo clone from American Type Culture Collection as a representative model of transepithelial barrier. The ability of cells to form a monolayer on a permeable support depends on the formation of tight junctions. Many
### TABLE 3

Properties and use of placental cell lines

<table>
<thead>
<tr>
<th>BeWo</th>
<th>Jeg-3</th>
<th>JAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin</td>
<td>Choriocarcinoma cells from BeWo</td>
<td>Choriocarcinoma cells derived from BeWo</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Not spontaneously differentiated</td>
<td>Not spontaneously differentiated</td>
</tr>
<tr>
<td>Hormonal secretion</td>
<td>Progesterone, hCG, steroids, (Morrish et al., 1997)</td>
<td>Progesterone, hCG, steroids, (Kato and Braunstein, 1991)</td>
</tr>
<tr>
<td>Ability to form confluent monolayer</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Use</td>
<td>Transplacental transport of drug</td>
<td>Gene expression</td>
</tr>
</tbody>
</table>

Factors such as the choice of media (essential nutrients and growth factors), seeding density, extent of cell confluency, exposure time, environmental conditions, and choice of permeable insert (diameter, pore size, supporting matrix) may influence tight junction development. Validity of the monolayer is assessed by measuring transepithelial electrical resistance and determining the transfer of paracellular markers (ulin, sucrose, fluorescein, fluorescein isothiocyanate-dextran, Lucifer yellow) (Liu et al., 1997; Konsoula and Barile, 2005). BeWo monolayers have been used for transport studies, but the latter report all different cell culture conditions (Saunders, 2009).

The BeWo cells consist of undifferentiated cytotrophoblasts with few syncytialized cells (Wice et al., 1990). Their differentiation into syncytiotrophoblasts does not occur spontaneously, but the syncytialization process can be induced by forskolin or 8-bromoadenosine 3',5'-cyclic monophosphate treatment (Borges et al., 2003). For this reason, BeWo cells are used for studies on the maturation of trophoblasts: they can model either cytotrophoblasts of early gestation or syncytiotrophoblasts of late gestation. Treatments with syncytium inducers result in an increase of monolayer permeability (Liu et al., 1997), which can be a disadvantage for transfer studies.

BeWo cells constitute a good model for studying the fusion process that occurs during syncytium formation. Envelope proteins such as syncytin-1, derived from human endogenous retroviruses, seem to play an essential role in these cellular fusion events (see the review by Pötgens et al., 2004). Syncytin-1 expression is up-regulated after stimulating the fusion of primary cytotrophoblast into syncytia by forskolin, a CAMP analog. Vargas et al. (2009) recently demonstrated a more important role for syncytin-2 in trophoblast fusion, showing that syncytin-1 expression changed slightly in BeWo on stimulation, compared with syncytin-2 fluctuation. Moreover, using two different targeted small interfering RNAs for each transcript, the authors demonstrated that a reduction of syncytin-2 expression led to a significant decrease in the number of BeWo cell fusions. Two amino acid transporters ASCT1 and ASCT2 expressed in trophoblast are potential receptors of syncytin-1. The receptor of syncytin-2 protein is also placenta-specific (Esnault et al., 2008).

ABC efflux transporters, including P-gp, MRPs and BCRP, are expressed in BeWo cells (Table 2). The pattern of expression is similar to that of syncytiotrophoblasts isolated from human placenta. BCRP is highly expressed in BeWo cells, whereas P-gp transcript and protein are minimally expressed or even absent. Both transporters are localized predominantly in the apical plasma membrane and show efflux activity. mRNA of MRP1, MRP2, MRP3, MRP5, and MRP8 are variably expressed, depending on differentiation status (Pascolo et al., 2000, 2003; Serrano et al., 2007). Folate transporters (Yasuda et al., 2008) and OCTN2 (Rytting and Audus, 2005, 2007) are present, whereas OAT and MCT expression has not been reported up to now. Expression of ABC transporters (BCRP, MRP1, MRP2) is modulated by cell differentiation (Evseenko et al., 2006b; Prouillac et al., 2009).

BeWo cells are stable, easily maintained by trypsinization, and form a confluent monolayer on a permeable support in a relatively short period of time (4–5 days). These advantages make this cell line an attractive in vitro model for studying trans-trophoblast transport and drug metabolism (Poulsen et al., 2009), as shown by numerous studies on the transport of digoxin, vinblastine, vincristine (Ushigome and drug metabolism (Poulsen et al., 2009), as shown by numerous studies on the transport of digoxin, vinblastine, vincristine (Ushigome et al., 2000), opioids peptides (Ampasavate et al., 2002), iron (Heaton et al., 2008), and cholesterol (Schmid et al., 2003) (Table 4).

**JAR and JEG-3 Cell Lines.** JAR and JEG-3 cell lines, derived from choriocarcinoma cell lines, are used in studies of placental function including differentiation, invasion, hypoxia/oxidative stress response, endocrinology, maternal fetal immunology, and transplacental transfer. The JEG-3 cells possess many of the biological and
biochemical characteristics of syncytiotrophoblasts, although they are mononucleated and proliferative (Matsuo and Strauss, 1994). They produce placental hormones (progestosterone, hCG, steroids) (Chou, 1982; Kato and Braunstein, 1991) and express various enzymes (Sun et al., 1998; Tremblay et al., 1999). Although they show biochemical differentiation, such as increased hCG secretion, JEG-3 cells do not morphologically differentiate with forskolin treatment (Al-Nasiry et al., 2006). However, JEG-3 cells have a lower rate of proliferation and a higher degree of differentiation than BeWo and JAR cells (White et al., 1988; Aplin et al., 1992; Borges et al., 2003; Kitano et al., 2004).

Compared with cytotrophoblast cells stemming from isolated human placenta, JAR cells are more similar to nondifferentiated cytotrophoblasts (Evseenko et al., 2006a). The JAR cell line is probably an unsuitable model for studies of transepithelial transport (Mitchell et al., 1995), exactly like JEG-3 cells, if one refers to the few studies reporting the use of JEG-3 as a model for vectorial transepithelial transport (Hardman et al., 2007). Indeed, the ability of both cell lines to form a polarized monolayer is controversial (Bode et al., 2006). The transcriptional profile and protein expression of many transporters, in particular export pumps (P-gp, MRPs, and BCRP) and organic anion transporters (OATPs), show quantitative variation in both cell lines (Table 2) (Serrano et al., 2007).

### Human Primary Cells

Primary cell lines of undifferentiated cytotrophoblasts can be produced from human placenta. Unless primary cells are allowed to differentiate, they represent early stages of gestation. These nonproliferative, multinucleated cells are able to syncytialize spontaneously. They form aggregates with large intercellular spaces, which make studies of polarized transport of xenobiotics impossible when they are grown on semipermeable membranes (Yui et al., 1994; Liu et al., 1997). Hemmings et al. (2001) reported that primary cytotrophoblasts formed tight junctions after three successive cycles of seeding and differentiation. Although this method produced multiple overlapping layers of syncytialized cells, areas of microvillar projections were formed on the apical surface and functioned as a barrier to low- and high-molecular-weight molecules. In addition to the fact that obtaining a reproducible cell population may be tricky, primary cell lines also have high contamination levels and are not viable for many passages. These cell lines are mostly used in investigations involving parasites or virus (Abbasi et al., 2003).

### Other Models for Placental Transfer Studies

Experimental models have to replicate the full features and functionality of in vivo trophoblast cells. For obvious ethical reasons, in vivo experimentation of placental drug transport in humans cannot be performed. Therefore, the risk assessment of fetal injury (teratogenic and fetotoxic potential of xenobiotics) from maternal exposure to xenobiotics is based on results from animal studies. Animal models provide the advantages of a complete physiological system. However, interspecies differences in placental morphology and length of gestation demand caution when assuming that the maternal-to-fetal transfer of substances observed in animal models will be observed in the same way in humans (Moe, 1995; Enders and Blankenship, 1999). For these reasons, mechanisms of placental transport, metabolism, and placental toxicity are best investigated in models of human origin (Myllynen and Vähäkangas, 2002). Primates such as rhesus macaques and baboons have also been used to evaluate the transfer of compounds because their hemochorial placentation is similar to that of humans (Patterson et al., 2000). An original study has recently reported the use of positron emission tomography imaging to monitor the placental...
P-gp function during pregnancy in nonhuman primates (Chung et al., 2010).

**Feto-Maternal Blood Concentration Ratio.** Human maternal and umbilical cord blood are simultaneously sampled during labor. Further analysis for the presence of compounds constitutes a simple and ethical method that illustrates the drug concentration between both circulations. However, the lack of comparison with a proper reference compound, the difficulties in evaluating the influence of placental metabolism on drug transfer, and the lack of information on drug distribution and accumulation in tissue are definite drawbacks (Levy, 1981; Waddell and Marlowe, 1981; Chamberlain, 1986; Simone et al., 1994).

**Human Coelocentesis.** This alternative to fetal blood sampling was introduced in 1991 (Jauniaux et al., 1991). It consists of sampling from human exocoelomic and amniotic fluid by transvaginal puncture at weeks 6 to 10 and weeks 7 to 12, respectively (Jauniaux and Gulbis, 2000). This method does not allow building a kinetic model, which is necessary to extrapolate quantitative drug transfer.

**Perfused Single Human Placental Cotyledon Model.** The technique of ex vivo perfusion of human placenta was first described by Panigel et al. (1967), then modified by Schneider et al. (1972). It is commonly used to investigate the mechanism and predict the rate of transfer of drugs through the placenta in vivo (Bourget et al., 1995). This model has been used to elucidate the mechanisms of placental transfer of HIV protease inhibitors and antiepileptic drugs (Forestier et al., 2001; Myllynen et al., 2003). Ethical problems are minimal because this technique is noninvasive and placentas are discarded or incinerated after birth. The critical point of the model is that it does not represent the first trimester placenta, when the fetus’ susceptibility to toxic hazards is high. However, because placental thickness and the number of cell layers decrease at the end of pregnancy, it is possible that the term placenta might be more sensitive to environmental agents than first anticipated (Vähäkangas and Myllynen, 2006). Another disadvantage is possible underestimation of the contribution made by transporters and metabolism during pregnancy, because transporters and metabolism differ between first trimester and full-term placenta. Interindividual variation also raises the question of the number of placentas that have to be perfused to validate the method. However, the influence of placental metabolism, the preferential direction of transport, and the presence of overall active transport can be evaluated. Results are generally compared with data on reference compounds such as inulin or antipyrine.

**Human Trophoblast Tissue Preparations.** Tissue explants can be used to study the transport of substances from the maternal circulation into the syncytiotrophoblast, as well as the metabolism, endocrine function, enzyme function, cellular proliferation, and differentiation in the placenta at early gestation or near term (Miller et al., 2005). This method requires careful consideration of the potential contribution of mesenchymal and endothelial cells to the metabolic process (Syme et al., 2004). Moreover, a recent publication has reported the limits of this model: the functional characterization of individual transporters is difficult, due to the lack of selective substrates and/or specific inhibitors. Furthermore, the authors suggested the presence of compensatory regulatory mechanisms, which could explain the difficulty of performing a good kinetic transfer study (Vaidya et al., 2009).

**Membrane Vesicles.** Isolated membrane vesicles can be obtained from either the membrane of the brush border or the basal surface of the trophoblast. Therefore, the study of transport mechanisms is possible in both fetal and maternal plasma membranes (Murcr and Kinne, 1980; Bissonnette, 1982). This model enables the characterization of expression and functionality (susceptibility to inhibitors, specificity, saturability) of transporters, but it does not reflect the in vivo situation, due to a lack of regulatory factors.

**Conclusions and Perspectives**

The expression of both ATP and SLC transporters has been demonstrated in many polarized epithelial barriers (i.e., kidney, liver, blood-brain barrier, intestine, lung, etc.) and many different species. Cellular localization combined with knowledge of the protein function gives insight into the role of these proteins in the accumulation and removal of specific substrates from the cells at each barrier. However, despite the considerable efforts invested in studying these transporters, few works have been dedicated to the cellular localization of these transporters in the placenta. Moreover, too little information is available on the mechanisms of fetal exposure to pollutants and the role of the placenta in this exposure.

First, placental models efficient for studying xenobiotic transport are far from being fully characterized. Better knowledge of cell properties (content in xenobiotic metabolism enzymes and transporters, number of passage, phenotype, differentiation) is required, and several external factors must be considered and optimized (Audus et al., 1990):

- culture conditions (culture medium composition, cell seeding density, stage of differentiation)
- permeable support characteristics (diameter, pore size, supporting matrix such as collagen)
- transport study conditions (transport medium composition, pH, temperature, etc.)
- diffusion apparatus (stirring or not)

In vitro placental transfer studies show high variability, occasionally leading to controversial results. Further investigation into transporter activity and membrane localization in the polarized placental epithelium will help to define the physiological and pharmacological functions of transporters in placental cells.

Second, the modulation of the expression of placental transporters may influence their role. In addition to variation of expression due to the gestation stage, in vivo genetic variability may also exist in xenobiotic transport by placenta. Variability is due to the presence of single nucleotide polymorphisms (SNPs), as has been shown for ABC transporter expression. This genetic polymorphism has been described for placental mdrl (Tanabe et al., 2001) and bcrp (Kobayashi et al., 2005) and is associated with altered P-glycoprotein expression (Hitzl et al., 2004). However, it remains to be determined whether these SNPs influence the pharmacokinetic and dynamic properties of clinically useful drugs. Rahi et al. (2008) reported that although SNPs altered the expression levels of P-gp in the human placenta, they did not have an effect on P-gp-mediated placental transfer of saquinavir. On the contrary, recent studies have shown that some homozygous mdrl variants (C1236T, C3245T) are associated with an increase in placental P-gp efflux of paclitaxel (Hemauer et al., 2010). Transfected cell lines expressing the polymorphic variant (Q141K) of ABCG2 exhibit altered placental pharmacokinetics of glyburide (Pollex et al., 2010). Further investigations are needed to define the significance of SNPs in the placental transport of xenobiotics.

Third, in addition to the trophoblast cells, human fetal membranes such as the amnion, chorion, and yolk sac may constitute an additional site of drug transfer in pregnant humans and rodents. Data are very scarce on transporter expression and function in these fetal annexes. The amnion can be considered as a barrier that separates maternal and fetal compartments and expresses functional transporter proteins such as MRPs and BCRP (Aye et al., 2007), as well as the chorion, which expresses BCRP (Yeboah et al., 2008). RFC protein is expressed in...
the yolk sac (Maddox et al., 2003), and the existence of xenobiotic efflux transporters in extraembryonic fetal membranes has recently been demonstrated in mice (Kalabis et al., 2007; Aleksunes et al., 2008). It is now necessary to study the contribution of fetal membranes in the transfer of xenobiotics between the mother and the fetus, which opens up a new field of research.

ABC and SLC proteins are able to transport nutrients as well as xenobiotics. These xenobiotics may compete with the physiological substrates of the placental transporters and interfere with the delivery of nutrients to the fetus. Future studies should deal with the possibility of an interaction that alters exchanges between fetus and mother. Exchange modulation may have long-term modulation of metabolic regulation and programming.

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