Human placental amino acid transporter genes: expression and function

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Recent findings on amino acid transporter genes are reviewed with particular focus on matching previously described transport systems to individual genes. Functional studies using cloned and expressed transporters are considered as the critical tool allowing identification of the functional properties of individual genes. Specifically, these experiments allow identification of the transported substrate amino acids and of the transport mechanism. We focus on the very recent discovery and properties of the heterodimeric family of amino acid transport proteins where two subunits encoded in different genes are required. For these transporters, co-expression of both subunits is mandatory for functional studies. The field of placental amino acid transport is further complicated by complexities arising from both gestational age-specific and species-specific gene expression. The function of the transporter also depends on its cellular localization in the trophoblast. In addition, for transporters that are coupled to ion gradients, both membrane potential and ion pumping will contribute to the rate of amino acid delivery to the fetus. Regulation of function is important not only for fetal nutrition but also for specific additional aspects of placental biology.

This short review attempts to place in context recent experimental work on amino acid transporters in human placenta. These transporters are of interest to reproductive biologists as through their integrated function they provide the fetus with the unique group of nutrients (amino acids) required for protein synthesis. Of the 20 amino acids that can charge specific tRNAs (and are thus necessary and sufficient for protein synthesis), some can be produced from precursors at rates sufficient to match their individual rate of utilization during synthesis of new protein. This is not true for the 'essential' amino acids, which must therefore be delivered to growing tissues if they are not to limit the rate of cellular protein synthesis. For normal growth in childhood, the group of such nutritionally essential amino acids is Arg, Val, His, Ile, Leu, Lys, Met, Phe, Trp and Thr. However, the high rates of protein synthesis that occur in the fetus *in utero* mean that the group of amino acids that must be delivered across the placenta will include others that may be non-essential in adult life. Thus, net transplacental delivery of this substantial group of amino acids to the growing tissues of the conceptus is essential for normal fetal growth and requires transporter gene expression, with appropriate synthesis and membrane insertion of these transporter (carrier) molecules. These amino acid transporters are not specific for one individual amino acid but instead recognize 'groups' of cognate amino acids (defined by the 'substrate specificity' of the individual transporter). Thus, transporters

may have overlapping specificities and an individual amino acid may be a substrate for several 'transport systems' (the phenotypic characterization of an individual transporter). Transport systems are characterized into those that are coupled to the electrochemical gradient of sodium ions through co-transport with Na⁺ ('sodium-coupled transporters') and those that are not ('sodium-independent transporters').

For cellular protein synthesis to proceed, all 20 tRNAs need to be charged simultaneously. Therefore, there must be homeostasis of the plasma concentrations of all 20 amino acids, and it is not surprising that a number of placental amino acid transporters function as 'exchangers' allowing movement across the plasma membrane of one amino acid in exchange for another. There is dispute about whether members of this group of transporters act solely as exchangers (that is, function as 'obligatory exchangers') or whether they can also produce the net transport of amino nitrogen required for fetal growth.

In humans, the placental barrier between maternal and fetal circulations is made by the trophoblast, which acts as an unusual epithelium separating the maternal circulation from the fetal circulation. The apical (brush border) membrane of the syncytiotrophoblast lies in direct contact with maternal blood, whereas the basal membrane of the trophoblast faces the fetal circulation flowing through the umbilical circulation in the placental chorionic villi. Co-ordinated activity of amino acid transporters in both of these membranes is required for net transport of amino acid across this epithelium.

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Table 1. Amino acid transport systems expressed by human placenta

Transport system	Gene	Substrates	Excludes	Localization	Reference	
					Transport activity	Gene/protein expression
Na ⁺ -dependent amino acid transport systems						
A	ATA1 (SLC38A1)	Neutral amino acids, MeAIB	Cationic and anionic amino acids, Leu, BCH	Apical/basal	Kudo <i>et al.</i> , 1987	Wang <i>et al.</i> , 2000
A	ATA2 (SLC38A2)	Neutral amino acids, MeAIB	Cationic and anionic amino acids, Leu, BCH	Apical/basal	Hoeltzli and Smith, 1989	Hatanaka <i>et al.</i> , 2000
ASC	ASCT1 (SLC1A4)	Ala, Ser, Cys, anionic amino acids	Cationic amino acids, Pro, MeAIB	Apical/basal	Kudo <i>et al.</i> , 1987	Arriza <i>et al.</i> , 1993
B ⁰	ASCT2 (SLC1A5)	Neutral amino acids,	Cationic and anionic amino acids, MeAIB	Basal	Hoeltzli and Smith, 1989	Kekuda <i>et al.</i> , 1996
N	SN1 (SLC38A3)	Gln, His	Cys, MeAIB	Apical	Karl <i>et al.</i> , 1989	
X _{AG} ⁻	EAAT1 (SLC1A3)	Anionic amino acids	Neutral and cationic amino acids	Apical/basal	Novak and Beveridge, 1997	
					Moe and Smith, 1989	
					Hoeltzli <i>et al.</i> , 1990	
Na ⁺ - and Cl ⁻ -dependent amino acid transport systems						
β	TAUT (SLC6A6)	β-Ala, Tau		Apical/basal	Karl and Fisher, 1990	Ramamoorthy <i>et al.</i> , 1994
B ^{0,+}	ATB ^{0,+} (SLC6A14)	Neutral and cationic amino acids	Anionic amino acids		Norberg <i>et al.</i> , 1998	
Gly	GLYT1 (SLC6A9)	Gly			Van Winkle <i>et al.</i> , 1990	
					Van Winkle <i>et al.</i> , 1988	
Cationic amino acid transport systems						
y ⁺	CAT1 (SLC7A1)	Cationic amino acids	Neutral and anionic amino acids	Apical	Eleno <i>et al.</i> , 1994	Kamath <i>et al.</i> , 1999
y ⁺	CAT2 (SLC7A2)	Cationic amino acids	Neutral and anionic amino acids			Kamath <i>et al.</i> , 1999
y ⁺	CAT4 (SLC7A4)	Cationic amino acids	Neutral and anionic amino acids	Basal	Ayuk <i>et al.</i> , 2000	Kamath <i>et al.</i> , 1999
Glycoprotein-associated amino acid transport systems						
asc	asc1/CD98 (SLC7A10/SLC3A2)	Small neutral amino acids	Cationic and anionic amino acids	nd		Fukasawa <i>et al.</i> , 2000
asc	asc2/unknown (SLC7A12?/unknown)	Small neutral amino acids	Cationic and anionic amino acids	nd		Chairoungdua <i>et al.</i> , 2001
b ^{0,+}	b ^{0,+} AT/rBAT (SLC7A9/SLC3A1)	Neutral and cationic amino acids, Cys	Anionic amino acids	Basal	Furesz and Smith, 1997	Feliubadalo <i>et al.</i> , 1999
L	LAT1/CD98 (SLC7A5/SLC3A2)	Large neutral amino acids	MeAIB	Apical	Kudo and Boyd, 2001b	Ritchie and Taylor, 2001
L	LAT2/CD98 (SLC7A8/SLC3A2)	Neutral amino acids	MeAIB	Basal	Kudo and Boyd, 2001b	Pineda <i>et al.</i> , 1999
y ⁺ L	y ⁺ LAT1/CD98 (SLC7A7/SLC3A2)	Neutral and cationic amino acids	Anionic amino acids	Basal/(apical)	Eleno <i>et al.</i> , 1994	Kudo and Boyd, 2000
					Ayuk <i>et al.</i> , 2000	

BCH: 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid; MeAIB: alpha-(methylamino)isobutyric acid; nd: not determined.

The topic of placental amino acid transporters has become of considerable recent interest in biomedical research because of the discovery of the effects of intra-uterine growth on postnatal development and associated patterns of adult morbidity and mortality (Godfrey and Barker, 2000; Barker, 2001). Moreover, placental amino acid transport is also implicated in aspects of development unrelated to fetal nutrition, for example, in trophoblast differentiation (Lavillette *et al.*, 2002) and in intra-uterine immunology (Kudo and Boyd, 2001a).

In this review, particular focus will be placed on studies in this area of research performed since the paper of Jansson (2001). There have been excellent general reviews on placental transporters, for example on transporters involved in transplacental drug delivery (Ganapathy *et al.*, 2000) and placental glucose transporters (Illsley, 2000), which are also relevant to the topic considered here.

Heterodimeric transporters

One of the particularly interesting developments in the area of amino acid transport has been the discovery of a family of dimeric proteins that catalyse, through their specific light chains, a wide spectrum of amino acid transport across the cell membrane of a wide variety of tissues including the human placental trophoblast. This family of molecules has been the subject of intense experimental work during the last 3 years following the pioneering description by Mastroberardino *et al.* (1998). This work has led to a flurry of reviews including those of Verrey *et al.* (2000), Devés and Boyd (2000), Kanai and Endou (2001), Chillaron *et al.* (2001), Wagner *et al.* (2001) and Meier *et al.* (2002). The known amino acid transporters in human trophoblast are shown (Table 1) and the properties of these transport systems are indicated with respect to substrate specificity and sodium dependence. The transport systems that are heterodimeric are also shown (Tables 1 and 2). Two heavy chains (either rBAT or CD98, known also as 4F2hc) form heterodimers with the family of light chains. The light chains specify the function of the transport complex, whereas the heavy chain appears to specify the apical or basal location of the transport system. In all epithelia studied to date the transporter complexes comprising rBAT as the heavy chain are localized to the apical membrane, whereas those in which CD98 (4F2) is the heavy chain are located basally.

In trophoblast, Ayuk *et al.* (2000) (see also Ayuk *et al.*, 2002) showed how different transporters contribute to transplacental cationic amino acid delivery. In the apical membrane transport system, γ^+ (encoded in genes of the CAT family) is the dominant pathway. This is a sodium-independent system that is electrogenic so that the membrane potential (inside negative) contributes to the uptake of this positively charged group of amino acids (lysine and arginine). In the basal membrane, the heterodimeric transporter encoding system γ^+L is predominant. (As this system has the unusual property of accepting charged

amino acids in the absence of sodium while also translocating neutral amino acids only when sodium is present, system γ^+L provides an effective electroneutral exit pathway for lysine and arginine.) However, in other epithelia in which system γ^+L also predominates in the basal plasma membrane, it is clear that the associated heavy chain is CD98. Thus, the immunocytochemical localization of CD98 in trophoblast is unexpected. Ayuk *et al.* (2000) showed by western blot analysis that this heavy chain, known to be required for γ^+LAT1 trafficking to the basal membrane in all other epithelia, was not detectable as antigen-displaceable immunoreactivity in basal plasma membrane preparations, but was detectable in the apical membrane vesicles. Okamoto *et al.* (2002) used immunohistochemistry and also found staining for this heavy chain at the apical surface. In contrast, using a different antibody (see Fig. 1) J. L. Millo and C. A. R. Boyd (unpublished) found strong basal staining for this heavy chain in term human placental villi. As Kudo and Boyd (2001b) showed that the amino acid transport system L was functionally detected in both isolated membrane vesicles prepared from the brush border and from basal surfaces, it appears that there is an important issue that remains to be resolved: that functional studies showed that the isoforms of system L in the brush border are distinct from those found in the basal membrane. Thus, system L in the brush border membrane behaved with the properties expected of the expressed amino acid transport system encoded by the LAT-1 light chain, whereas the basal surface behaved with the properties expected of the LAT-2 light chain. Specifically, small neutral amino acids such as alanine were inhibitors of basal transport only (see Fig. 2). Such findings raise a question: how can a single heavy chain (CD98) transport different light chains to different membranes? As both LAT1 and LAT2 transport only with CD98, it follows that something is lacking in our understanding of the process of system L isoform distribution in the human trophoblast. Is it possible that CD98 heavy chain is not the only heavy chain expressed in the trophoblast? This proposal is not implausible given the intriguing recent finding that three novel light chains, asc2 (Chairoungdua *et al.*, 2001), AGT1 (Matsuo *et al.*, 2002) and XAT (Blondeau, 2002), are expressed in mouse kidney transport with a novel, as yet unknown, heavy chain that is neither CD98 nor rBAT. The conflicting reports concerning the immunolocalization of CD98hc might have a ready resolution if the antibodies used in the studies of J. L. Millo and C. A. R. Boyd (unpublished) and Okamoto *et al.* (2002) do not or do crossreact, respectively, with the proposed missing heavy chain. It is interesting that a similar discrepancy in the literature concerning localization of the $Na^+-K^+-ATPase$ in trophoblast appears to have been resolved in recent careful studies showing isoform localization to both membranes (Persson *et al.*, 2002).

What might be the function of heterodimeric amino acid transporters in placenta? Meier *et al.* (2002) have shown that system L (both isoforms) appears to perform only coupled transport in an oocyte expression system. Although

Fig. 1. Immunohistochemistry of CD98 in chorionic villi of human term placenta. (a) Trophoblast shows prominent immunoreactivity at the basal surface of the syncytium as well as less prominent staining of the apical surface (J. L. Millo and C. A. R. Boyd, unpublished). (b) Trophoblast shows immunoreactivity at the apical surface of the syncytium as well as less prominent staining of the basal surface. (Reproduced with permission from Okamoto *et al.*, 2002.) Scale bar represents 20 μ m.

Table 2. Light chains for the heterodimeric amino acid transport systems expressed by human placenta

Light chain	Transport system	Localization	Transport function	Reference	
				Transport activity	Gene/protein expression
Light chain associated with CD98					
LAT1	L	Apical	Na ⁺ -independent: large neutral amino acids	Kudo and Boyd, 2001b	Mastroberardino <i>et al.</i> , 1998 Richie and Taylor, 2001
LAT2	L	Basal	Na ⁺ -independent: large and small neutral amino acids	Kudo and Boyd, 2001b	Pineda <i>et al.</i> , 1999
y ⁺ LAT1	y ⁺ L	Basal/(apical)	Na ⁺ -independent: cationic amino acids Na ⁺ -dependent: large neutral amino acids	Ayuk <i>et al.</i> , 2000	Torrents <i>et al.</i> , 1998
asc1	asc	nd	Na ⁺ -independent: small neutral amino acids D-isomers of small neutral amino acids		Fukasawa <i>et al.</i> , 2000
Light chain associated with rBAT					
b ^{0,+} AT	b ^{0,+}	Basal	Na ⁺ -independent: neutral and cationic amino acids, cysteine	Furesz and Smith, 1997	Feliubadalo <i>et al.</i> , 1999
Light chain associated with unknown heavy chain					
asc2	asc	nd	Na ⁺ -independent: small neutral amino acids		Chairoungdua <i>et al.</i> , 2001

nd: not determined.

their striking results fit with the known strong exchange properties characteristic of 'native' system L as established in many functional studies during the last 20 years (for an example, see Shotwell *et al.*, 1983), their findings indicate that system L cannot generate net transport of amino acids across the placenta. However, because oocyte studies must necessarily be performed at a temperature lower than that in mammalian tissue *in vivo*, it is still appropriate to be somewhat guarded in excluding the possible role of heterodimeric transporters in achieving net rather than exchange transport. Thus, early work on leucine transport in red blood cells (Hoare, 1972) showed that temperature was a major

factor influencing exchange versus net capability. Moreover, the experiments of Segawa *et al.* (1999), who found net amino acid efflux through LAT-2 co-expressed (in oocytes) with CD98, are in contrast to the findings of Pineda *et al.* (1999) and Meier *et al.* (2002). This discrepancy indicates that it will be important not to overlook the possibility that additional factors (for example, regulatory proteins) might be required for net transport through system L in placenta as in other epithelia.

System L (for a review, see Wagner *et al.*, 2001) has a possible additional role in placental biology. System L amino acid transporters may couple changes in extracellular tryp-

Fig. 2. Functional analysis of tryptophan influx through system L into isolated (a) apical or (b) basal membrane vesicles. Note the inhibition by small neutral amino acids, such as alanine and serine, in basal but not in apical membranes, showing the functional fingerprint of the light chain LAT2 in basal and LAT1 in apical membranes (Redrawn from Kudo and Boyd, 2001b).

tophan (outside the trophoblast in the maternal intervillous space) to indoleamine 2,3-dioxygenase (IDO)-mediated tryptophan degradation within the trophoblast. The seminal study of Munn *et al.* (1998) established (in mouse) the importance to reproductive immunology of IDO-mediated specific depletion of this particular amino acid. These authors showed that when this catabolic pathway was disrupted pharmacologically (with 1-methyl-tryptophan, a specific inhibitor of IDO), normal implantation and subsequent successful pregnancy did not occur. However, this effect was confined to allogeneic matings producing conceptuses able to express distinct paternally inherited alleles. In syngeneic matings, 1-methyl-tryptophan was without effect, but when such syngeneic conceptuses were transgenically manipulated to express immunologically distinct surface antigens, the IDO inhibitor was able to abrogate successful implantation.

Subsequent work by Kudo and colleagues (for a review, see Kudo and Boyd, 2001a) indicated that a similar mechanism might occur in established human pregnancy, as all the component mechanisms established for IDO-mediated immunosuppression of the maternal immune response against the fetus in mice are also found in human placenta. This finding indicates that inhibitors of system L amino acid transport in human placenta (for example, by 2-amino-bicyclo-(2,2,1)-heptane-2-carboxylic acid (BCH)) might, like 1-methyl-tryptophan (by inhibiting the normal maternal immune response), be effective abortifacients. At the earliest stages of implantation, van Winkle (2001) has suggested that systems B^{0,+} and b^{0,+} might be important for tryptophan transport and for access of 1-methyl-tryptophan to IDO.

Sodium-coupled transporters

There has been important recent work on amino acid transporters other than those that are heterodimeric. Cramer *et al.* (2002) have shown that system A is important for fetal growth in rats, as when it was inhibited by a competitive non-metabolized substrate infused into the mother during days 7–20 of gestation, fetal growth was significantly decreased. System A has been cloned from the placenta (Wang *et al.*, 2000) and the importance of this transporter to mammalian pregnancy supports earlier work showing that the rate of system A-mediated amino acid transport in the placenta of babies with intra-uterine growth retardation is significantly reduced. Thus, uptake of non-metabolized amino acid (aminoisobutyric acid AIB or methyl-AIB) into brush membrane vesicles of placentae from such pregnancies was significantly reduced compared with controls (Dicke and Henderson, 1988; Mahendran *et al.*, 1993). In the work of Mahendran *et al.* (1993), the effect on system A amino acid transport was apparently specific, as other systems studied did not show this effect. Since these papers were published, further studies have demonstrated altered amino acid transport in placentae associated with growth-restricted babies (Glazier *et al.*, 1997; Godfrey *et al.*, 1998; Jansson *et al.*, 1998; Norberg *et al.*, 1998).

Glutamate transport has also been studied in rodent models and rat placental transport of this amino acid appears to be predominately through system X_{AG}⁻ (Matthews *et al.*, 1998, 1999), the role of which in placenta has up until now been studied little. It will be interesting to determine whether regulation of system X_{AG}⁻ in placenta involves amino acid response elements linked to amino acid deprivation, as described by Franchi-Gazzola *et al.* (1996).

Sodium-independent transporters

System y⁺ has been studied in placenta by Ayuk *et al.* (2000) and the underlying molecular processes are reviewed by Closs (2002). There are various isoforms of system y⁺, specifically CAT-1, CAT-2 and CAT-4, and all three of these genes are expressed at the mRNA level in human placenta (Kamath *et al.*, 1999). It is interesting that this system, which catalyses the uptake of the essential cationic acids (lysine, arginine and histidine) is sodium-independent yet electrogenic. The straightforward explanation for this (see Devés and Boyd, 1998) is that translocation of the substrate itself generates current flow; hence, the membrane potential (trophoblast inside negative, see Birdsey *et al.*, 1999) provides the driving force for accumulation of such amino acids. The mechanism by which these cationic amino acids leave across the trophoblast basal membrane requires a different system, as here the trophoblast potential will oppose rather than aid movement of such cations across the cell membrane. That this is the site of functional expression of the amino acid transporter system y⁺L (originally described in red blood cells (Déves *et al.*, 1992) and more recently in human placenta (Eleno *et al.*, 1994; Ayuk *et al.*, 2000)) and that this transport system is electroneutral provides a ready solution to this conundrum. In fact, system y⁺L is a transporter for cationic amino acids that is able to exchange these cationic amino acids against sodium-coupled neutral amino acid flux (for example, glutamine, leucine), providing a natural route for efflux across epithelial cell membranes, as originally proposed by Boyd (1992) and subsequently confirmed by Pineda *et al.* (1999) and Kanai *et al.* (2000). System y⁺L is a member of the CD98 heterodimeric transporter family (Table 2) and these findings support further investigation into the nature and distribution of the heavy chain family in placenta.

Conclusion

Constancia *et al.* (2002) have shown that delivery of alpha-(methylamino)isobutyric acid (alpha-methyl-AIB) through system A to the fetus is reduced when the paternally expressed insulin-like growth factor II gene is deleted. This finding indicates that this imprinted gene controls the placental supply of maternal nutrients to the mammalian fetus. Therefore, it will be important to investigate the molecular mechanisms altering system A transporter activity, as these must be involved in the processes by

which maternal–paternal genetic conflict is both generated and regulated. It will also be interesting to determine whether other placental transporters, including those reviewed here, are similarly regulated through this or other paternally imprinted genes. Other areas that need further work include changes in amino acid transport during development, particularly in the early stages of implantation. Study of how the expression of different transporter genes is coordinated is also lacking. It is striking that at the present no abnormal phenotype is related to abnormalities of amino acid transporter genes, emphasizing the importance of future studies that bring together cell biologists and clinical obstetricians.

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