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Review

Omega-3 fatty acids transport through the placenta

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Abstract: The placenta is a temporary vital organ for sustaining the development of the fetus throughout gestation. Although the fatty acid composition delivered to the fetus is largely determined by maternal circulating levels, the placenta preferentially transfers physiologically important long-chain polyunsaturated fatty acids (LC-PUFAs), particularly omega-3 (n-3) FAs. The precise mechanisms governing these transfers were covered in a veil, but have started to be revealed gradually. Several evidences suggest fatty acid transport proteins (FATPs), placental specific membrane bound fatty acid binding proteins (pFABPpm) and fatty acid translocases (FAT/CD36) involved in LC-PUFAs uptake. Our studies have shown that the placental transfer of omega-3 FAs through the trophoblast cells is largely contributed by fatty acid binding protein 3 (FABP3). Recently there are considerable interests in the potential for dietary omega-3 FAs as a therapeutic intervention for fetal disorders. In fact, prenatal supply of omega-3 FAs is essential for brain and retinal development. Recent findings suggest a potential opportunity of omega-3 FA interventions to decrease the incidence of type 2 diabetes in future generations. In this review, we discuss the molecular mechanism of transportation of omega-3 FAs through the placenta and how omega-3 FAs deficiency/supplementation impact on fetal development.

Keywords: Omega-3 fatty acids; FABP3; placenta; fetal development; trophoblast

1. Introduction

The placenta is the principal site of nutrient exchange between the mother and the fetus. Survival and growth of the fetus are critically dependent on the placenta. Trophoblast cells fuse to form a syncytium, resulting in a two layered structure of multinucleated syncytiotrophoblast (SCTB) and cellular cytotrophoblast. Protusions of SCTB interdigitate into the decidualised endometrium, forming contacts with the maternal blood supply (Frost and Moore, 2010). Nutrients must cross through the multilayer trophoblast cells which separates the fetal capillary from the maternal sinusoids (Watson and Cross, 2005). Placental nutrient uptake and transfer have a unique role in the fetal development, as changes in nutrient-dependent signaling pathways in placental trophoblast leads to the alteration of fetal cell metabolism and may affect the fetal growth and the health programming after birth (Jansson *et al.*, 2013; Jansson and Powell, 2013).

Fatty acids are the source of energy, constitute a vital structural component of cellular membranes, and are precursors for important bioactive compounds. Among the fatty acids, long-chained polyunsaturated fatty acids (PUFAs) are crucially important for the proper development of different tissues and organs. For instance, PUFAs are required for proper brain development (Joffre *et al*., 2014; Larque *et al.*, 2012; Makrides *et al.*, 2011; Watanabe *et al.*, 2007). During late gestation, the neonate′s brain experiences a tremendous increase in growth

and cellular proliferation. For this rapidly growing infant, there is a high demand for complex lipids, such as docosahexaenoic acid (DHA, 22:6n-3) to form vital cell membrane structures. Human fetuses have a limited ability to synthesize omega-3 LCPUFA *de novo* and have to be supplied via maternal sources (Joffre *et al*, 2014). Other studies evaluating the early exposition to PUFAs, in particular omega-3 PUFAs, showed benefits in the offspring development and epigenetic regulation, which seem to prevent obesity, insulin resistance and cardiovascular diseases onset (Mennitti *et al*, 2015). Therefore, elucidating the pathways of placental omega-3 FAs transport and the regulatory processes governing these pathways are critical for advancing our understanding about the relationships between maternal omega-3 FAs metabolism and the placental supply of metabolites to the developing fetus. In this review, we would summarize recent development in the biochemical processes involved in placental omega-3 FAs delivery to the fetus. In accordance with this, we would show the impact of deficiency/supplementation of omega-3 FAs on the fetus.

2. Structure of the human placenta

Placenta is directly responsible for bringing maternal and fetal blood supplies into contact, facilitating nutrient exchange and determining resource allocation (Frost and Moore, 2010). Human have an invasive hemochorial placenta resulting in close opposition of fetal and maternal blood and cells (Krishnan *et al.,* 2013). The human placenta is a villous organ, whereby maternal blood comes into direct contact with placental trophoblast cell. The intervillous space is completely lined with a multinucleated syncytium called SCTB (Figure 1). Circulating maternal blood enters the intervillous space via spiral endometrial arteries, bathes the villi and drains back through endometrial veins. (Gude *et al.,* 2004). Protrusions of SCTB interdigitate into the endometrium, forming contacts with the maternal blood supply. Interstitial trophoblast cells invade to expand the placenta from its edge outwards (Frost and Moore, 2010). Initially, the placental membrane is made up of four layers, the maternal facing SCTB, a layer of cytotrophoblast cells, connective tissue of the villus and the endothelium lining the fetal capillaries (Figure 1a). By approximately 20 weeks of gestation, the cytotrophoblast cell layer of many villi becomes attenuated and disappears gradually (Figure 1b). Subsequently, in most of the chorionic villi, the membrane consists of three layers and, in some areas, becomes extremely thin such that the SCTB comes in direct contact with the fetal capillary endothelium (Gude *et al.,* 2004). The SCTB constitute the transporting epithelium of the placenta, with two polarized membranes, the microvillous membrane (MVM) facing maternal circulation and the basal plasma membrane (BM) facing the fetal capillary (Figure 1b). After passage across the SCTB membranes, substrates must cross the second layer of cells, the fetal capillary epithelium, before entry into the fetal circulation is complete. Only smaller solutes are highly permeable through the MVM and BM, and thus the SCTB constitutes a barrier and rate-limiting step of the transport of nutrients into fetal circulation (Brett *et al.,* 2014).

3. Molecular mechanism of omega-3 FAs transport

3.1. Transport of omega-3 and other FAs through the placenta

All of the PUFAs accumulated in the fetus must be obtained from the mother by placental transfer (Innis, 2005), predominantly originate from two sources in maternal circulation: nonesterified fatty acids (NEFAs) and esterified fatty acids in triglycerides (TGs) carried by lipoproteins (LPs) (Haggarty, 2010) (Figure 2). Fatty acids cannot cross the placenta in the form of TGs, therefore they must be converted to NEFAs by hydrolysis. This enzymatic process of TGs conversion is accomplished by several lipases expressed in the MVM (Lindegaard *et al.,* 2006). Among the several lipases, lipoprotein lipase (LPL) and endothelial lipase (EL) have been well studied in the MVM. In addition to the LPL and EL activity, TG hydrolase expression and activity also exist in the MVM of human placenta (Waterman *et al.,* 1998; Waterman *et al.,* 2000) which is also involved with the conversion of TGs to NEFA. The hydrolysis of TGs by lipase or hydrolase appears to be of critical importance for the supply of LC-PUFA available for fetal transport (Benassayag *et al.,* 1997). The placenta lacks the enzymes Δ5- and Δ6-desaturase which are involved in the conversion of NEFA or essential fatty acids (EFA) to LC-PUFA must be supplied from mother (Hanebutt *et al.,* 2008; Wadhwani *et al.,* 2013; Mennitti *et al*, 2015). TGs and NEFA after conversion into LC-PUFA are ready to cross the lipid bilayer of SCTB cells (Figure 2).

3.2. Transporters of fatty acids

Transfer of fatty acids from maternal space to fetal circulation may be regulated by the maternal to fetal concentration gradient (Haggarty, 2010). Some fatty acids can cross the lipid bilayer of SCTB cells by simple diffusion, however, due to high fetal demand of fatty acids, the trophoblast cells have protein mediated transportation (Figure 2) (Kazantzis and Stahl, 2012). Several evidences support the selective transport mechanism of PUFAs in cell culture models (Campbell *et al.,* 1997; Tobin *et al.,* 2009) and perfused placenta

(Haggarty *et al.,* 1997), as well as from *in vivo* studies with DHA labeled with stable isotopes (Gil-Sanchez *et al.,* 2010). Among the several membrane proteins, fatty acid transport proteins (FATPs, also known as SLC27A) are familiar for its cellular uptake of LC-PUFAs (Kazantzis and Stahl, 2012). Out of six family members of FATPs, FATP1-4 and FATP6 are expressed in both human and mouse placenta (Schaiff *et al.,* 2005; Schaiff *et al.,* 2007). FATP1 has been detected at protein level of both the MVM and the BM (Campbell *et al.,* 1998; Duttaroy, 2009). Recently, FATP1 and FATP4 have been found to be involved in fatty acid uptake (Zhan *et al.,* 2012). FATP4 is found to be highly expressed by the epithelial cells of the visceral endoderm of the yolk sac and localizes at the brush-border membrane of extraembryonic endodermal cells (Gimeno *et al.,* 2003). FATP4 gene deletion model shows early embryonic lethality (Gimeno *et al.,* 2003), thus suggesting a critical role in materno-fetal fatty acid transport during early embryogenesis. In cultured trophoblast cells from term placenta, peroxisome proliferator-activated receptor (PPAR)γ/retinoid X receptor signaling and hypoxia regulate FATP4 mRNA expression (Mishima *et al.,* 2011; Schaiff *et al.,* 2005). Besides FATPs, two other membrane fatty acid transporters- namely, placental specific membrane bound fatty acid binding protein (pFABPpm) and fatty acid translocase (FAT/CD36) are involved in fatty acid uptake in the placenta (Campbell *et al.,* 1998) (Figure 2). pFABPpm is exclusively expressed in the MVM (Campbell *et al.,* 1998). Functionally, pFABPpm exhibits a high affinity for LC-PUFAs, suggesting this transporter to be involved in preferential uptake of these fatty acids for transfer across the placenta (Campbell *et al.,* 1997). Recent study using an epithelial cell line has demonstrated that while comparing the efficacy to uptake fatty acids, FAT/CD36 is found to be 30 fold higher than that of FATP4. FAT/CD36 may directly facilitate fatty acid transport across the plasma membrane, whereas the intracellular FATP4 enhance fatty acid uptake indirectly by metabolic trapping in epithelial cells (Schneider *et al.,* 2014). Since trophoblast cells are epithelial in character expressing both the FAT/CD36 and FATP4, similar mechanism of fatty acid uptake in the plasma membrane is possible.

After entering into the cytosol of SCTB cells, cytoplasmic fatty acid binding proteins (FABPs), traffic the fatty acids to sites for fatty acid uptake and metabolism, storage, beta-oxidation, signal transduction, ligand activation or transfer to the fetus (Owada, 2008) (Figure 2). Out of 12 members of FABPs family, FABP1, FABP3, FABP4, FABP5 and FABP7 have been observed to occur in both human and rodent placenta (Biron-Shental *et al.,* 2007; Daoud *et al.,* 2005; Das *et al.,* 1993; Knipp *et al.,* 2000; Larque *et al.,* 2006; Masouye *et al.,* 1997; Watanabe *et al.,* 1991). In our study, FABP3, FABP4, FABP5 and FABP7 have been found to be spatially localized throughout rodent placenta, suggesting that functional properties may differ from each other depending on their localization (Islam *et al.,* 2014). In our study, FABP3 gene deletion model shows significant down regulated transportation of omega-3 FA compared to wild type fetus. Similar observation has also been demonstrated by human trophoblast cell line. Our data suggest FABP3 regulates omega-3 FA transport in trophoblasts and plays a pivotal role in fetal development (Islam *et al.,* 2014). In addition to FABPs and FATPs, exploring other molecules involved in fatty acid metabolism have been described, i.e. microsomal triglyceride transfer protein and apolipoprotein B (Farese *et al.,* 1996; Raabe *et al.,* 1998).

4. Impact of omega-3 FAs deficiency/supplementation on fetus

LC-PUFA, particularly DHA is an important constituent of the phospholipids of all cell membranes, where they play roles assuring the correct environment for membrane protein function, maintaining membrane fluidity, regulating cell signaling, gene expression and cellular function, and serving as substrates for the synthesis of lipid mediators (Calder, 2012). Over the past decades, evidences from observational studies and randomized trials have suggested that the intake of LC-PUFA throughout pregnancy, particularly DHA, plays potential benefits on maternal and fetal/neonatal health (Mozurkewich and Klemens, 2012). About 60% of the dry weight of brain tissue is fat; DHA and arachidonic acid (AA) are the most abundant LC-PUFA in the brain and are critical for proper brain, nervous system and eye development (Morse, 2012). Considerable amounts of fatty acids accumulate in the fetal brain cortex tissue and retinal membrane synapses during the third trimester of pregnancy and during the first postpartum month (Dziechciarz *et al.,* 2010; Gould *et al.,* 2013). Data from large cohort studies as well as from randomized controlled trials indicates that an adequate amount of omega-3 FAs is important for the neonate to support long-term cognitive and visual development (Larque *et al.,* 2012). Several observational studies also show that omega-3 FAs supplementation in pregnancy or in lactation improve child visual and cognitive outcomes (Gould *et al.,* 2013). Animal studies using mouse model also support the hypothesis for the contribution of omega-3 FAs in fetal development. Chunyu and his colleagues fed mice with omega-3 FA diets from two months before conception and throughout lactation, resulting in the elevated levels of expression of neuron-specific enolase, glial fibrillary acidic protein and myelin basic protein and the expression of PPARγ, which is activated by fatty acid ligands, was also increased in the pup brain (Tian *et al.,*

2011). These results suggest that the higher intake of omega-3 FAs during both maternal pregnancy and lactation may be beneficial for early brain development.

Gestational diabetes is a common pregnancy complication affecting 3.5% to 7.2% of pregnancies (Bardenheier *et al.*, 2013). LC-PUFA is fundamental to the functional integrity of pancreatic beta-cells (Dixon *et al.*, 2004; Konard *et al.*, 1996). A growing body of evidence suggests that fatty acid nutritional status in early life affects fetal tissue lipids as well as neuroendocrine and metabolic pathways relevant to metabolic ‘‘programming’’ (Korotkova *et al.*, 2005). Babies of gestational diabetic mothers have reduced DHA in the plasma and erythrocyte cholinephosphoglycerides. The total omega-3 fatty acids of the erythrocyte cholinephosphoglycerides are significantly lower in these babies (Min *et al.*, 2005). Recent studies have revealed that low circulating fetal DHA levels are associated with compromised fetal insulin sensitivity, and may be involved in ‘‘programming’’ the susceptibility to type 2 diabetes in the offspring of gestational diabetic women. These findings suggest a potential opportunity of early life nutritional interventions (e.g. DHA supplementation) to halt adverse metabolic programming to decrease the incidence of type 2 diabetes in future generations (Zhao *et al.*, 2014).

Pregnancy has been suggested to be a critical period for developmental programming, which may influence the later development of allergic diseases in childhood (Prescott, 2010). Maternal diet, especially maternal PUFA intake, during pregnancy may modify neonatal immune response through epigenetic mechanisms and therefore alter disease susceptibility and predisposition (Calder *et al.*, 2010; Prescott, 2010). The mechanism of anti-allergic reaction of omega-3 FAs in neonate is still not clear. However, it is proposed that a higher intake of omega-3 FA, for example, by fish oil supplementation, may have protective effects against the development of atopic diseases in the offspring although not all studies show conclusive results (Calder *et al.*, 2010; Kremmyda *et al.*, 2011; Larque *et al.*, 2012).

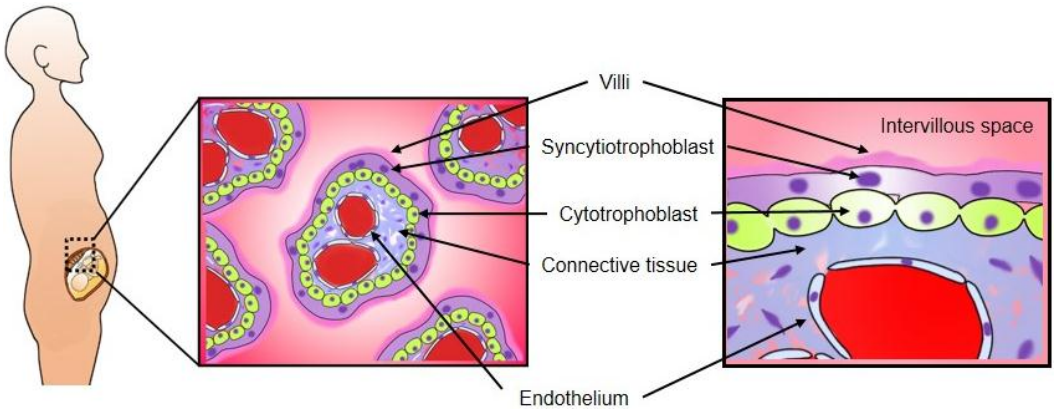

Figure 1a. Trophoblast layers in human placenta at 20 weeks of gestation. The placental membrane is made up of four layers, the maternal facing SCTB, a layer of cytotrophoblast cells, connective tissue of the villus and the endothelium lining the fetal capillaries.

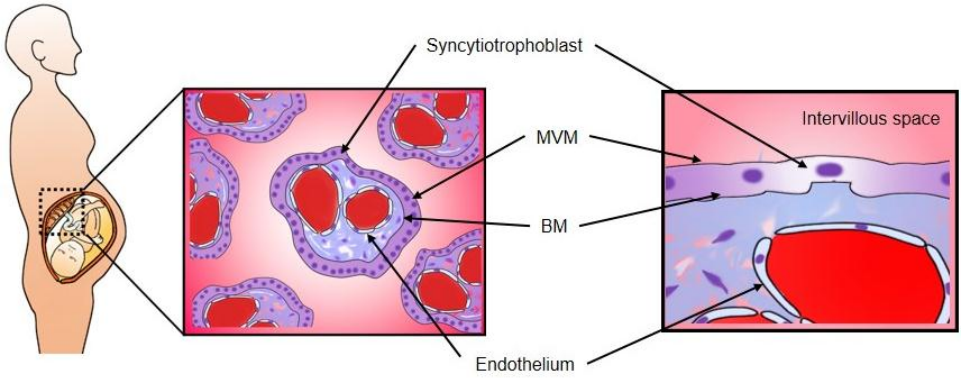

Figure 1b. Trophoblast layers in human placenta at the end of pregnancy. The cytotrophoblast cell layer of many villi becomes attenuated and disappears. Subsequently, in most of the chorionic villi, the membrane consists of three layers and, in some areas, becomes extremely thin such that the SCTB comes in direct contact with the fetal capillary endothelium. The SCTB constitute the transporting epithelium of the placenta, with two polarized membranes, the microvillous membrane (MVM) facing maternal circulation and the basal plasma membrane (BM) facing the fetal capillary.

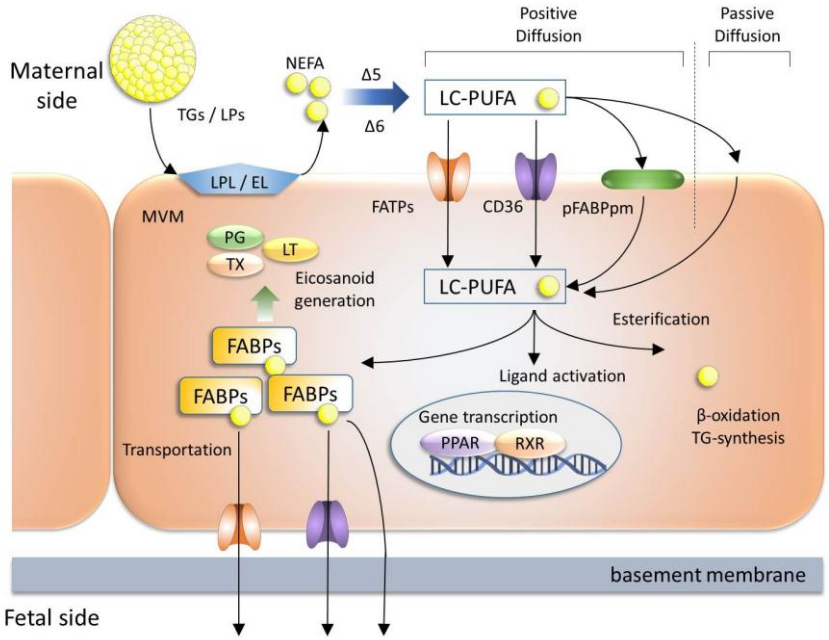

Figure 2. Transport of fatty acids across the SCTB. A model of placental fatty acid transport through SCTB is shown. A complex interplay of different fatty acid transport proteins orchestrates fatty acid uptake mechanism. Within the cells LC-PUFAs are bound by different FABPs and have multiple functions like eicosanoid and TG synthesis, activation of nuclear transcription factors like PPAR/RXR and energy generation. Some LC-PUFAs are transported to fetal side through transporters. EL; endothelial lipase, FATP; fatty acid transport protein, FAT; fatty acid translocase, LC-PUFA; long chain polyunsaturated fatty acid, LP; lipoprotein, LPL; lipoprotein lipase, LT; leukotriene NEFA; non-esterified fatty acid, p-FABPpm; placental plasma membrane FABP, PG; prostaglandin, PPAR; peroxisome proliferator activated receptor, RXR; retinoid X receptor, TG; triglyceride, TX; thromboxane. [Figure was modified from Hanebutt *et al.*, 2008].

5. Conclusions

Alterations in fetal development and growth have been closely associated with lifelong adverse health consequences. Since fetal growth and placental fatty acid transport are closely linked, a cohesive knowledge of placental nutrient transport mechanism will most certainly bring us closer to understanding those mechanisms underlying altered fetal growth. As reviewed in this paper, research has predominantly focused upon how the fatty acids, especially omega-3 FAs are transported through placental barrier (SCTB). Several recent studies resulted in the discovery of novel mechanisms involved in the regulation of placental nutrient transport. However, further work is needed to elucidate how fetal, maternal, and placental signals are integrated, regulate omega-3 FA transport from mother to fetus, and impact on fetal development ultimately.

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Conflict of interest

None to declare.

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