Advances in Animal Fatty Acid Transmembrane Transport Proteins FATP1 and FATP4

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Abstract: Fat is the main composition of the body, it not only has an important role to maintain the animal’s physiological function but also its precipitation and sedimentary parts have became the key factor to influence the carcass and meat quality. As two members of the family of the fatty acid transport proteins, FATP1 and FATP4 involved in the transport of long chain fatty acids across the plasma membrane and the metabolism of fatty acids. They are the key genes which have an influence on fat content and maintain skin phospholipids metabolism. So, in this study, the characteristic of structure, function and variation of the gene FATP1 and FATP4 have been summarized. Researchers hope this content can provide certain reference for the researchers in the future.

Key words: FATP1, FATP4, function, polymorphism, plasma membrane, China

INTRODUCTION

Long-Chain Fatty Acids (LCFAs) are not only extremely important in the human diet but they also play an important role in the pathogenesis of fluid accumulation, the production and storage of metabolic energy, the synthesis of the cell membrane and the anchoring functions of proteins. A number of proteins have found to be possibly involved in the uptake of LCFAs. These include Fatty Acid Translocase (FAT/CD36), Fatty Acid Binding Protein (FABP), long-chain Acyl-Coenzyme A Synthetase (ACSL), Acyl-CoA Binding Protein (ACBP) and Fatty Acid Transport Protein (FATP) (Coburn et al., 2001; Chiu et al., 2001; Glatz et al., 2002; Stahl, 2004). Despite the fact that all these proteins have some role in the uptake and metabolism of LCFAs, recent studies have found that FATPs play any important role in the uptake and metabolism of fatty acids or in the maintenance of epidermal phospholipid metabolism and composition. In this project, researchers performed a comprehensive overview of two main members of the FATPs family: FATP1 and FATP4. This study provides information that may promote in-depth understanding of the characteristics and mechanisms of FATP1 and FATP4 and the development of strategies for treating fat metabolism related diseases.

AN OVERVIEW OF THE FATPS FAMILY

The FATP family also known as Solute carrier family 27 (Slc27) includes six different members, each with different expression patterns in different tissues though, most of them affect fatty acid. FATP1, a major family member of FATP in the adipose tissue (Schaffer and Lodish, 1994) is expressed in the heart and skeletal muscle (Schaffer and Lodish, 1994; Binnert et al., 2000; Pohl et al., 2000). Stahl et al. (2002) found that insulin could induce mouse FATP1 to move from the cell kernel cavity to the plasma membrane and the degree of insulin-induced FATP1 translocation was consistent with increases of LCFAs uptake. This indicated that hormone-regulated FATP1 activity may play a very important role in the maintenance of a stable energy state within the internal environment. FATP4 which is closely related to FATP1 is highly expressed in the small intestine, adipose tissue, skin, heart and liver (Stahl et al., 1999, 2001; Hermann et al., 2001, 2003). It is also the only member of the FATP family that is expressed in the small intestine. By analysis of the effects of FATP4 overexpression in cells and of the isolated intestinal epithelial cells, it has been found that FATP4 plays an important role in the absorption of LCFAs by the intestinal epithelial cells. FATP2, FATP3, FATP5 and FATP6 are more distantly related to FATP1 and show little or no expression in fat tissue and muscle. Briefly, FATP2 is highly expressed in the liver and kidneys (Hirsch et al., 1998). FATP3 is expressed in the liver, pancreas and lungs (Stahl et al., 2001). FATP5 is expressed only in the liver (Hirsch et al., 1998). FATP6 is mainly expressed in the heart (Gimeno et al., 2003a, b).
FATP LOCATION AND STRUCTURE

**FATP1 gene location and structure:** FATP is an integral membrane protein. Analysis of the membrane topology of FATP1 has shown that a short N-terminal fragment is located outside of the cell membrane bilayer and the C-terminus is located in the cell cytoplasm. All members of the FATP family have an AMP-binding protein sequence located within the first 300 amino acids of the FATP signal sequence. Researchers initially analyzed the hydrophobicity of amino acid sequence of the *FATP* gene using the Kyte-Doolittle Method and proposed that this gene might have six transmembrane domains (Lewis et al., 2001). In 2000, the human FATP1 gene was cloned. It is located on Chromosome 19 and it consists of 12 exons and 11 introns. It contains six hydrophobic transmembrane domains and three potential glycosylation sites (Martin et al., 2000). Song et al. (2008) successfully cloned the fowl FATP1 gene which has an open reading frame of 1941 bp encoding 646 amino acids. Currently, most of the mammalian FATP1 genes have been cloned. Amino acid sequence analysis has revealed >87% of homology between mammalian FATPs but only 71-74% homology between poultry and mammalian FATPs.

**FATP4 location and structure:** FATP4 is also a member of the FATP family. It is closely related to FATP1. It was not investigated in depth until it was found to be involved in the fatty acid uptake and transport and to play an important role in lipid metabolism. Thomas et al. (2001) cloned the mouse FATP4 gene which is located on Chromosome 2 using an open reading frame of 1929 bp, encoding 643 amino acids. The human FATP4 gene contains 12 exons, located on Chromosome 9, encoding a protein of 71 kDa in molecular weight (Herrmann et al., 2001). The protein contains a conserved AMP-binding protein sequence which is common to all FATPs family members.

The mRNA sequences of many animal FATP4 genes have been reported, most of them in mammals including humans, cattle, ratten and brown rats. Sequence alignment analyses have shown >85% of sequence homology between mammals. However, the mRNA and protein sequences of the non-mammalian FATP4 genes from such animals as fish and poultry have not yet been recorded in public gene databases.

**MECHANISMS OF FATPS**

The mechanisms underlying the actions of FATP-family proteins in the uptake of LCFAs remain unknown. There is also, a question of whether FATP1 plays the role of transporter or promotes the accumulation of fatty acids in cells by preventing the release of LCFAs. Four controversial models of the mechanisms of FATP have been proposed (Doege and Stahl, 2005). The first model assumes that FATPs are the only transmembrane transport proteins that indirectly regulate the absorption of LCFAs and that they are associated with other proteins such as ACSLs (Richards et al., 2006). The second model assumes that the FATPs themselves are the long-chain, membrane-bound proteins and act as long-chain acyl-coenzyme A synthetases causing LCFAs to become involved in cell manipulation and diffuse through the cell membrane. The third model assumes that FATPs act either through a transport role, through an acyl-coenzyme A role or through a combination of the two. The fourth model assumes that FATPs are multifunctional proteins that can indirectly regulate the absorption of LCFAs rather than rely on their esterification role. The results of Schaffer and Lodish (1994) support the first model. This study confirmed that FATP1 forms ACSL heterodimers in adipose cells (Richards et al., 2006). Schaffer and Lodish (1994) deem that the intake of LCFAs is required for all of the proteins. This model is consistent with the results obtained from a study of the uptake of fatty acids in an *E. coli* system using a combination of the transport protein FadL, Fad and acyl coenzyme A synthetase (DiRusso and Black, 1999; DiRusso et al., 2005). However, supporters of the second model deem that the purified FATPs have ACSL activity. FATP-mediated absorption of LCFA may be driven by increasing the transformation of the fatty acids located within the bilayer leaflets to fatty acyl coenzyme A. Yeast expression experiments have confirmed the third model. Specific mutations in the *FATP* gene can identify the input of fatty acids in acyl-coenzyme A synthetase activity indicating that this protein has two independent functions in yeast. Because these existing mechanisms are still controversial, further investigation into the structure and function of FATP is required before a more accurate transport mechanism model can be proposed.

**Role of FATP1:** To date, many studies have shown that FATP1 plays an important role in the transport and metabolism of fatty acids in vivo. Over expression of FATP1 in the cardiocytes of transgenic mice can increase the uptake of myocardial fatty acids and the accumulation of free fatty acids but cannot change the triglyceride level. This causes lipotoxicity cardiomyopathy by increasing the oxidation of palmitic acid (Kim et al., 2004; Chiu et al., 2005). Over expression of FATP1 in skeletal muscle can increase the transport of LCFAs and induce the oxidation of these lipids but it does not affect the accumulation of
intramuscular fat (Holloway et al., 2011). Wu et al. (2006a) found that insulin cannot effectively stimulate the adipocytes lacking FATP1 to absorb fatty acids. However, the absorption of basal LCFA As remained unaffected by the absence of FATP1. Schaffer and Lodish (1994) reported that the mouse 3T3-L1 fat precursor cells stably transfected with the FATP1 gene could transport oleic acid 4-5 times faster than the control group. In a study of the FATP1 protein function Lobo et al. (2007) found that knocking out the FATP1 gene could significantly reduce the deposition of the triglyceride in adipocytes. García-Martínez et al. (2005) found that overexpression of FATP1 in the sarcotubules of human skeletal muscle could promote fatty acid uptake and storage but would not be oxidized. In addition, FATP1 has been shown to be involved in the process of hormone-regulated fatty acid uptake and response to insulin in adipose cells and original skeletal muscle cells by changing the plasma and other components (Stahl et al., 2002; Wu et al., 2006b).

FATP1 has specific selectivity in the transport of LCFA As. Schaffer showed that FATP1 mainly mediated the transmembrane transport of fatty acids whose backbone lengths are >10 carbon atoms such as myristic acid (C14:0), palmitic acid (C16:0) and oleic acid (C18:1) but had no effect on the transmembrane transport of short-chain fatty acids (Schaffer and Lodish, 1994).

FATP1 also affects energy metabolism. Wu et al. (2006a, b) found that FATP1 played a role in nonshivering thermogenesis in adipose tissue. In 2009, Mitchell and Guitar independently found that FATP1 could regulate the re-synthesis of cardiolipin and increase pyruvate dehydrogenase activity (Guitar et al., 2009; Mitchell and Hatch, 2009). Recently, Sebastian et al. (2009) found that the use of adenovirus to overexpress FATP1 in the L6E9 sarcotubule could increase the oxidation of fatty acids and the esterification of palmitate in triglycerides indicating that FATP1 might be associated with mitochondria and fatty acid oxidation therein (Mitchell and Hatch, 2009).

Role of FATP4: FATP4 (SLC27A4) is the only member of the FATP family that is expressed in the small intestine, mainly in the brush edge of intestinal epithelial cells (Stahl et al., 1999). It has a very important role in the transmembrane transport of LCFA As. Because FATP4 is involved in dietary lipid intake, it may be a suitable anti-obesity target.

In addition, FATP4 plays an important role in the maintenance of the epidermal phospholipid component, phospholipid metabolism and maintenance of normal skin function Moulson et al. (2003) and Hermann et al. (2003) found that newborn mice with homozygous deletions of FATP4 had similar phenotypes, specifically tight, thick skin, broken skin barriers, facial deformities and dyspnea but their ability to absorb LCFA As was unaffected (Hermann et al., 2003; Moulson et al., 2003). Gimeno et al. (2003a) found that the deletion of exons 1 and 2 in the mouse FATP4 gene would result in embryo lethality in the 1st 9.5 days of pregnancy (Gimeno et al., 2003b). The deletion of exon 3 in the mouse FATP4 gene however, resulted in hyperkeratotic skin and damage to epidermal barrier function (Jia et al., 2007). However, increased expression of FATP1 in the dermis and FATP5 and CD36 in the epidermis was found to promote the repair of the permeability barrier.

POLYMORPHISMS OF FATPS

Association of the FATP1 and FATP4 polymorphisms with human obesity and related conditions: The polymorphisms of FATP1 are mainly associated with dyslipidemia. Meihaeghe et al. (2000) identified three Single Nucleotide Polymorphisms (SNPs) in introns 8 and 9 in 1144 French individuals. This was the first study to indicate an association between FATP gene polymorphisms and changes in the internal human lipid internal environment. These results suggested that FATP1 polymorphisms might affect lipid metabolism. Gertow et al. (2003) analyzed the same A/G polymorphism in exon 8 in 856 Swedish individuals. In contrast to the results of the Meihaeghe study, no significant association was found between FATP1 polymorphism and fasting plasma Triglyceride (TG) content. However, the associations between FATP1 polymorphism and postprandial cholesterol and the distribution of particle sizes of low-density lipoproteins were found to be significant.

FATP4 is also associated with human pathophysiology. Bower found that in obese African American and Caucasian women increased mRNA and protein levels of FATP4 in adipose cells were associated with a higher LCFA absorption. Gertow et al. (2004) investigated 17 pairs of monozygotic twins with different Body Mass Indexes (BMI) and different levels of obesity and insulin resistance and found that there was more FATP4 mRNA expression in patients with more pronounced obesity and that this was not associated with genetic factors. Gertow found that the polymorphism in exon 3 of FATP4 resulted in an amino acid exchange within the FATP4 protein and caused insulin resistance syndrome. These findings suggest that these allele carriers have lower metabolic parameters including BMI, TG insulin levels and systolic blood pressure than carriers with homozygous normal G/G alleles.
Association between FATP1 polymorphisms and economically relevant traits in livestock and poultry:

There are only a limited number of studies on FATP1 gene polymorphisms in livestock and poultry. Using DNA sequencing and Restriction Fragment Length Polymorphism (RFLP), Hua et al. (2011) identified two mutations (g.586T>C and g.601A>G) in the pig FATP1 gene. The g.586T>C genotype was found to be significantly associated with shoulder and back fat thickness, average back fat thickness and leaf fat weight indicating that this mutation might affect pig fatty deposition. Ordovas et al. (2008) identified 14 SNPs in Holsteins using minisequencing. However, these SNPs did not significantly affect the level of cow milk fat, suggesting that FATP1 has little or nothing to do with milk fat content. Lv et al. (2010) reported that the C allele of T112C in the Holstein FATP1 gene had no positive effect on milk production, suggesting that FATP1 may affect the milk yield of the Chinese Holstein. Using the PCR-SSCP Method, Wang et al. (2010) identified five mutations in the chicken FATP1 gene. These mutations were significantly associated with some carcass traits and abdominal fat weight indicating that the FATP1 gene has some impact on abdominal fatty deposition in chickens.

CONCLUSION

FATP1 and FAPT4 are two important members of the FATPs family, each of which has specific, important biological functions. FATP1 is mainly involved in fatty acid and energy metabolism. It also has an important role in the treatment of fatty deposition, obesity and Type II diabetes. FAPT4 mediates keratinocyte uptake of LCFA and provides the keratinocytes with raw materials for synthesis of phospholipids. FATP4 also has an important role in the treatment of skin diseases. Although, preliminary studies have been performed for some members of the FATP family, there are only a few reports on the effects of FATP1 and FAPT4 on the quality of animal meat and on fat and skin diseases. This is why it is important to study the associations between genetic variations of FATP1 and meat quality and fatty deposition and the role of FAPT4 in the skin under normal physiological and pathological conditions.

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REFERENCES


