Gene Section
Review

**FABP5 (fatty acid binding protein 5 (psoriasis-associated))**

Erin Balcom, Rong-Zong Liu, Stanley Poon, Roseline Godbout

Department of Oncology, University of Alberta, Cross Cancer Institute, 11560 University Avenue, Edmonton, Alberta, T6G 1Z2 Canada (EB, RZL, SP, RG)

Published in Atlas Database: August 2014
Online updated version: http://AtlasGeneticsOncology.org/Genes/FABP5ID49862ch8q21.html
DOI: 10.4267/2042/62185

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2015 Atlas of Genetics and Cytogenetics in Oncology and Haematology

**Abstract**

The FABP5 gene encodes a member of the fatty acid binding protein family which is also known as epidermal or cutaneous FABP. Overexpression of FABP5 is associated with a number of cancers including breast and prostate cancers, as well as psychiatric disorders and diabetes. FABP5 can bind retinoic acid as well as polyunsaturated and saturated fatty acids. Transport of FABP5 ligands such as arachidonic acid and retinoic acid to the nucleus is believed to activate the nuclear receptor peroxisome proliferator-activated receptor beta/delta (PPARβ/δ).

**Keywords**

Fatty acid binding protein 5, fatty acids, retinoic acid, peroxisome proliferator-activated receptor, breast cancer, prostate cancer, glioma, pancreatic cancer, diabetes, psychiatric disorders, psoriasis, obesity

**Description**

The FABP5 gene spans approximately 4.3 kb and has 4 exons, all of which contain coding sequences. Ten SNPs have been validated in the coding region of FABP5, 7 missense and 3 synonymous (not affecting the amino acid sequence).

Two SNPs in the regulatory region of FABP5 have been identified in association with type 2 diabetes mellitus (T2DM): rs454550 showed significant association with T2DM in a non-Hispanic White sample, and a newly reported SNP at genomic position 82354416 was associated with T2DM in both non-Hispanic White and African sample populations (Bu et al., 2011).

A missense 340G>C (Gly114Arg) SNP in the coding region of FABP5 has been linked to autism (Maekawa et al., 2010). FABP5 SNPs are described at the following site (http://www.ncbi.nlm.nih.gov/snp).

**Transcription**

The transcript is approximately 750 nucleotides with an open reading frame of 408 nucleotides, a 5' untranslated region of 113 nucleotides and a 3' untranslated region of 209 nucleotides excluding the poly-A tail.

**Identity**

**Other names:** E-FABP, EFABP, KFABP, PAFABP

**HGNC (Hugo):** FABP5

**Location:** 8q21.13

**Local order:** PAG1 → FABP5 → PMP2.

**DNA/RNA**
FABP5 (fatty acid binding protein 5 (psoriasis-associated))

Balcom E, et al.

Atlas Genet Cytogenet Oncol Haematol. 2015; 19(7)

434

FABP 5 gene. The FABP5 gene is located on chromosome 8 in the region of q21.13 on the positive strand. Neighbouring genes are indicated.

Based on Expressed Sequence Tag (EST) data, FABP5 RNA is present in a wide range of human tissues, with highest levels in the uterus, pharynx, bone, and heart. FABP5 transcripts have been identified in normal mammalian cells, including adipocytes, tongue epithelia, lens (Wen et al., 1995), developing retina, lung and mammary gland epithelia (Zimmerman and Veerkamp, 2002), macrophages, kidney, liver, and skeletal muscle (Smathers and Petersen, 2011). Immunohistochemistry has confirmed the presence of FABP5 in endothelial cells of the placenta, heart, small intestine, and renal medulla (Masouyé et al., 1997).

Nerve growth factor (NGF) positively regulates FABP5 expression in PC12 cells (pheochromocytoma of rat adrenal medulla) through a MEK-dependent pathway (Liu et al., 2008). FABP5 is a known target of c-Myc (Coller et al., 2000), and epithelial cell adhesion molecule epCAM has been demonstrated to upregulate FABP5 expression, presumably via induction of c-Myc (Münz et al., 2005).

The promoter region of FABP5 contains two cognate response elements (CREs) to transcription factor NF-κB (Kannan-Thulasiraman et al., 2010). Epidermal growth factor receptor (EGFR) activation directly increases FABP5 expression through the ERK and phosphatidylinositol-3-kinase cascades and subsequent activation of NF-κB (Kannan-Thulasiraman et al., 2010). Ligands of peroxisome proliferator-activated receptors (PPARs) have been shown to influence FABP5 expression: PPARα and PPARγ agonists upregulate FABP5 expression, whereas PPARβ activation decreases FABP5 expression (Hyder et al., 2010). In contrast to FABP7, mRNA length for FABP5 does not vary throughout the body, limiting the likelihood of post-transcriptional modification (Zimmerman and Veerkamp, 2002).

Pseudogene

The human genome contains 14 pseudogenes similar to the FABP5 locus. Predicted pseudogenes are listed here: http://www.ncbi.nlm.nih.gov/gene/?Term=related_functional_gene_2171%5Bgroup%5D.

Protein

Description

FABP5 is a member of the intracellular lipid binding protein family. FABP5 is a 135 amino acid protein with an estimated molecular mass of 15.1 kDa. Similar to other FABPs, FABP5 has a beta-clam (beta barrel) structure composed of 10 anti-parallel beta sheets and two N-terminal alpha helices, with low backbone motility (Gutiérrez-Gonzalez et al., 2002). Six cysteine residues and a disulfide bridge between Cys120 and Cys127 contribute to protein stability and are hypothesized to relieve oxidative stress by thiol disulfide interchange reaction (Odani et al., 2000). Hydrophobic ligands are bound within the water-filled central cavity formed by the beta barrel. The carboxylic head group of linoleic acid forms a salt bridge with Arg-129 and hydrogen bonds with the hydroxyl groups of Tyr-131 and Arg-109 in the binding pocket of FABP5 (Armstrong et al., 2014). Hydrophobic residues within the binding pocket such as Cys-120 also facilitate ligand binding. FABP5 contains ligand-sensitive tertiary nuclear
FABP5 (fatty acid binding protein 5 (psoriasis-associated))

Balcom E, et al.

Expression
FABP5 was first identified as a low molecular weight protein highly upregulated in human psoriatic skin (Madsen et al., 1992). FABP5 is expressed in numerous normal adult epithelial tissues, including those of the reproductive and urinary tracts, mammary glands, lungs, tongue, and lens. FABP5 is also expressed in macrophages, bone, and skeletal muscle (Smathers and Petersen, 2011). The expression of FABP5 during mammalian neurogenesis has been investigated using rodent models, with similar results obtained in mouse and rat. FABP5 transcripts are detected in mid-term embryonic rat brain, peaking at birth and gradually decreasing from P1 to P21, with expression virtually undetectable in the adult brain (Owada et al., 2002), except during regeneration in response to neuronal injury (Allen et al., 2001). FABP5 is critical in post-natal hippocampal dentate gyrus neurogenesis in mice (Matsumata et al., 2012).

Localisation
The FABP5 protein has a nuclear or cytoplasmic localization that is dependent upon ligand binding and cell type. Retinoic acid (RA), linoleic acid and arachidonic acid (AA) have been shown to elicit nuclear translocation through allosteric interaction between the ligand-sensing β2 loop and nuclear localization sequence (NLS) in the α1 helix (Tan et al., 2001; Schug et al., 2007; Armstrong et al., 2014).

Function
Unique to brain-expressed FABPs, both human and rat FABP5 have a high affinity for saturated fatty acids such as stearic acid, with a Kd of 168.1 nM as determined by 1-anilinonaphthalene-8-sulfonic acid (ANS) assay (Liu et al., 2010), and 290 nM as determined by the Lipidex assay (see Table) (Liu et al., 2010). FABP5 has a broad range of saturated and unsaturated hydrophobic ligands, including linoleic acid, eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), AA and their derivatives (Sanson et al., 2014). Nuclear localization upon binding to linoleic acid and AA is thought to influence gene expression through activation of the nuclear receptor PPARβ/δ (Tan et al., 2001), which controls the expression of genes involved in lipid and glucose metabolism, differentiation, and survival (Schug et al., 2007). FABP5 expression during development is associated with neurite outgrowth (Allen et al., 2001), with an important role in post-natal hippocampal dentate gyrus neurogenesis through nuclear transport of RA to activate PPARβ/δ (Matsumata et al., 2012). The hippocampi of FABP5-null mice contain excess neuronal progenitors and are deficient in mature neurons (Yu et al., 2012). FABP5 knockout mice do not have a brain phenotype, perhaps as a result of compensation by other FABP members.

Homology
The human FABP5 amino acid sequence is 64.8% identical to chicken FABP5 and 80% identical to mouse FABP5 isoform 1. Human FABP5 shows variable sequence identity with the other FABP paralogs, with the highest identity to FABP8/PMP2 (59%) and the lowest identity to FABP2 and FABP6 (27%). FABP5 is phylogenetically related to FABP3 and FABP7, which are also expressed in the brain (Schoentgen et al., 1989; Godbout, 1993; Bennett et al., 1994; Feng et al., 1994) and shows 51% and 46% amino acid sequence identity with FABP3 and FABP7, respectively. FABP5 also has sequence identity to other lipid binding proteins, with 36% identity to human cellular retinoic acid binding protein 1 (CRABP1).
FABP5 (fatty acid binding protein 5 (psoriasis-associated))


<table>
<thead>
<tr>
<th>Fatty Acid Classification</th>
<th>Fatty Acid</th>
<th>Kd (nM)</th>
<th>Method</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ω-3 fatty acids</td>
<td>Docosahexaenoic Acid (DHA; 22:6)</td>
<td>422 ± 58.1 (Rn)</td>
<td>ANS</td>
<td>Liu et al. 2008</td>
</tr>
<tr>
<td>ω-6 fatty acids</td>
<td>Eicosapentaenoic Acid (EPA; 20:5)</td>
<td>898 ± 100.3 (Rn)</td>
<td>ANS</td>
<td>Liu et al. 2008</td>
</tr>
<tr>
<td></td>
<td>Arachidonic Acid (AA; 20:4)</td>
<td>390.9 ± 54.2 (Rn)</td>
<td>ANS</td>
<td>Liu et al. 2008</td>
</tr>
<tr>
<td></td>
<td>Linoleic Acid (LOA; 18:2)</td>
<td>1730 ± 250 (Rn)</td>
<td>Lipidex</td>
<td>Holeff et al. 1999</td>
</tr>
<tr>
<td></td>
<td>Linoleic Acid (LOA; 18:2)</td>
<td>318 ± 14 (Ms)</td>
<td>ANS</td>
<td>Kame et al. 1996</td>
</tr>
<tr>
<td>Monounsaturated fatty acid</td>
<td>Oleic Acid (OA; 18:1)</td>
<td>154 ± 35.3 (Rn)</td>
<td>ANS</td>
<td>Liu et al. 2008</td>
</tr>
<tr>
<td></td>
<td>Palmitoleic Acid (PA; 16:1)</td>
<td>1081 ± 370 (Rn)</td>
<td>Lipidex</td>
<td>Shimamoto et al. 2014</td>
</tr>
<tr>
<td></td>
<td>Linoleic Acid (LOA; 18:2)</td>
<td>248 ± 12 (Ms)</td>
<td>ANS</td>
<td>Kame et al. 1996</td>
</tr>
<tr>
<td>Saturated fatty acids</td>
<td>Stearic Acid (SA; 18:0)</td>
<td>250 ± 60 (Hs)</td>
<td>Lipidex</td>
<td>Holeff et al. 1999</td>
</tr>
<tr>
<td></td>
<td>Myristic Acid (MA; 14:0)</td>
<td>1409 ± 23 (Ms)</td>
<td>ANS</td>
<td>Kame et al. 1996</td>
</tr>
<tr>
<td>Other</td>
<td>All-trans Retinoic Acid (ATRA)</td>
<td>3690 (Ms)</td>
<td>ANS</td>
<td>Kame et al. 1996</td>
</tr>
<tr>
<td></td>
<td>Retinoic Acid</td>
<td>34.8 ± 6.6</td>
<td>ANS</td>
<td>Schug et al. 2007</td>
</tr>
</tbody>
</table>

Ligand affinities for FABP5. Abbreviations: Rn= Rattus norvegicus, Ms= Mus musculus, Hs= Homo sapiens.

Mutations

Note

Several variants of FABP5 have been linked to human diseases, including type 2 diabetes. Nine MGI mutant phenotypes in mice have been reported, with disruption in FABP5 resulting in defects in epithelial water balance and resistance to obesity.

Implicated in Cancer

FABP5 is involved in signaling pathways controlling differentiation, metabolism, proliferation, and resistance to apoptosis (Tan et al., 2001) and is highly expressed in several human tumors including breast, prostate, oral, and hepatocellular carcinomas (Adamson et al., 2003; Fujii et al., 2005; Fang et al., 2010). The majority of malignancies associated with elevated FABP5 are of apparent epithelial origin, where FABP5 is believed to contribute to proliferation, metastasis, and resistance to therapy.

Breast cancer

In 2001, FABP5 overexpression was shown to induce metastasis in rat mammary epithelial cells through induction of the vascular endothelial growth factor (VEGF) (Jing et al., 2001). FABP5 can also be upregulated by EGFR signaling in breast cancer cells and serves as a critical mediator of EGFR-induced cell proliferation (Kannan-Thulasiraman et al., 2010). Analysis of a cohort of 120 breast cancer patients revealed an association between elevated levels of cytoplasmic FABP5, high tumor grade, reduced recurrence-free survival and poor prognosis in triple-negative breast cancer (Liu et al., 2011) (see Figure). Recently, genetic ablation of FABP5 was shown to suppress Her-2-induced mammary tumorigenesis, indicating a potential role for FABP5 as a chemotherapeutic target (Levi et al., 2013). Manipulation of FABP5 levels in human breast cancer cell lines and cell lines generated from breast cancer mouse models demonstrates a correlation between FABP5 levels and response to RA treatment (Schug et al., 2007; Schug et al., 2008; Liu et al., 2011). It has been hypothesized that FABP5 confers resistance to RA therapy through competition with CRABP2 for RA, with FABP5 promoting proliferation and survival through activation of PPARβ and CRABP2 inhibiting proliferation through activation of the nuclear retinoic acid receptor (RAR) (Schug et al., 2007; Schug et al., 2008; Liu et al., 2011).
**Prostate cancer**

Elevated FABP5 protein levels are linked to increased tumor size and invasiveness in prostate cancer (Adamson et al., 2003). Depletion of FABP5 decreases VEGF and microvessel density in prostatic tumors in nude mice and suppresses proliferation and invasion in prostatic carcinoma cells (Adamson et al., 2003). High levels of FABP5 are associated with a poorer prognosis in prostate cancer (Morgan et al., 2008; Forootan et al., 2014). Significantly higher levels of FABP5 protein were found in the serum of patients with lymph node metastatic prostate cancer compared to patients with localized prostate cancer (Pang et al., 2010). As in other cancers, FABP5 appears to influence tumor progression through PPARβ, and levels of both FABP5 and PPARβ correlate with the tumorigenic potential of prostate cancer cell lines by inducing the expression of genes which promote anchorage independence and proliferation (Morgan et al., 2008). FABP5 has been shown to be a direct target of PPARβ in prostate cancer cell lines and it has been suggested that targeting the PPARβ/FABP5 pathway may represent a new strategy for the treatment of prostate cancer (Morgan et al., 2008).

**Other cancers**

FABP5 is elevated in several other human malignancies where it influences tumorigenic potential by modulating proliferation, invasion, and drug resistance. Cytoplasmic FABP5 levels are elevated in human head and neck squamous cell carcinomas (Han et al., 2009). Elevated cytoplasmic FABP5 levels have also been documented in advanced tongue carcinomas (Ohyama et al., 2014).

Proteomic analysis revealed FABP5 as highly upregulated in oral squamous cell carcinoma (OSCC). Overexpression of FABP5 increased invasion, proliferation and production of matrix metalloproteinase-9 (MMP-9) in OSCC cell lines (Fang et al., 2010). Drug-resistant adenocarcinoma of the pancreas is associated with high levels of FABP5, with FABP5 proposed to facilitate the sequestration and removal of cytotoxic drugs in these tumors (Sinha et al., 1999). In keeping with other types of cancers, a high ratio of FABP5 to CRABP2 in pancreatic ductal adenocarcinoma cell lines correlates with poor response to RA, whereas CRABP2 expression in the absence of FABP5 correlates with growth inhibition in the presence of RA (Gupta et al., 2012).

A number of RA signaling proteins, including FABP5, are highly expressed in high-grade astrocytomas, with FABP5 expression correlating with an undifferentiated tumor phenotype (Campos et al., 2011). The ratio of FABP5 to CRABP2 was found to correlate with survival time in grade IV astrocytoma patients, with a high FABP5 to CRABP2 ratio associated with shorter term survival (Barbus et al., 2011).

**Psychiatric diseases**

Abnormalities in lipid metabolism are linked to several psychiatric illnesses. Several rare non-synonymous polymorphisms in FABP5 have been identified in patients with schizophrenia and autism spectrum disorder. Altered FABP5 mRNA expression levels were detected in schizophrenic brain (Shimamoto et al., 2014). Variants in the FABP5 gene were found in autistic patients, but no significant genetic association between FABP5 and autism has been established (Maekawa et al., 2010).
**Obesity, metabolic syndrome, atherosclerosis**

Due to their role in lipid homeostasis, FABPs have been implicated in obesity, metabolic syndrome, and atherosclerosis. Increased serum levels of FABP5 correlate with age, waist circumference, blood pressure, and insulin resistance in human adults (Ishimura et al., 2013). Combined deficiency in FABP5 and FABP4 in mice protects against atherosclerosis and metabolic syndrome (Babaev et al., 2011). In a population study of 806 individuals with type 2 diabetes, levels of FABP4 and FABP5 in adipocytes and macrophages independently correlated with incidence of metabolic syndrome and the presence of coronary artery calcium, a marker for coronary heart disease (Bagheri et al., 2010). FABP4 and FABP5 may contribute to the pathogenesis and serve as biomarkers for metabolic syndrome and cardiovascular disease risk factors.

**Diabetes**

Two single nucleotide polymorphisms in the regulatory region of FABP5 are associated with type 2 diabetes in humans (Bu et al., 2011). Human islet cells and insulin-secreting rat INS1E β-cells express FABP5 (Hyder et al., 2010). Targeted depletion of FABP5 protected mice from insulin resistance and diabetes when administered a high fat diet (Maeda et al., 2011). High glucose increased FABP5 expression in human islet and rat β-cells, indicating that FABP5 contributes to pancreatic function and glucose metabolism in mammals (Hyder et al., 2010).

**Psoriasis**

FABP5 was first identified as a gene highly upregulated in human psoriatic skin lesions (Madsen et al., 1992). Psoriasis is caused by a defect in the differentiation of keratinocytes, and FABP5 modulates differentiation of normal and psoriatic human keratinocytes (Dallaglio et al., 2013). It has been proposed that FABP5 overexpression contributes to the pathogenesis of psoriasis by promoting the proliferation and survival of keratinocytes and disrupting the uptake and metabolism of fatty acids in the epidermis. In psoriasis patients, depletion of FABP5 in the epidermis upon TNF-α or narrow-band ultraviolet B treatment corresponded with response to therapy (Miyake et al., 2012).

**References**


Schug TT, Berry DC, Shaw NS, Travis SN, Noy N. Opposing effects of retinoic acid on cell growth result from alternate activation of two different nuclear receptors. Cell. 2007 May 18;129(4):723-33


Schug TT, Berry DC, Toshkov IA, Cheng L, Nikitin AY, Noy N. Overcoming retinoic acid-resistance of mammary carcinomas by diverting retinoic acid from PPARbeta/delta to RAR. Proc Natl Acad Sci U S A. 2008 May 27;105(21):7545-51


Miyaue T, Ogawa E, Mikoshiba A, Kobayashi A, Hosoe H, Kashiwabara S, Ubara H, Owada Y, Okuyama R. Epidermal-type FABP is a predictive marker of clinical

Yu S, Levi L, Siegel R, Noy N. Retinoic acid induces neurogenesis by activating both retinoic acid receptors (RARs) and peroxisome proliferator-activated receptor β/δ (PPARβ/δ). J Biol Chem. 2012 Dec 7;287(50):42195-205


Yu S, Levi L, Casadesus G, Kunos G, Noy N. Fatty acid-binding protein 5 (FABP5) regulates cognitive function both by decreasing anandamide levels and by activating the nuclear receptor peroxisome proliferator-activated receptor β/δ (PPARβ/δ) in the brain. J Biol Chem. 2014 May 2;289(18):12748-58

This article should be referenced as such: