EDITORIAL

Fatty acid binding receptors in intestinal physiology and pathophysiology

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Abstract

Free fatty acids are essential dietary components and recognized as important molecules in the maintenance of cellular homeostasis. In the last decade, the molecular pathways for free fatty acid sensing in the gastrointestinal tract have been further elucidated by molecular identification and functional characterization of fatty acid binding receptors. These sensing molecules belong to the family of G protein-coupled receptors. In the intestine, four important receptors have been described so far. They differ in molecular structure, ligand specificity, expression pattern, and functional properties. In this review, an overview of intestinal fatty acid binding receptors and their role in intestinal physiology and pathophysiology is given.

Key words: G protein; Intestine; Free fatty acid; Receptor

INTRODUCTION

Free fatty acids (FFAs) and their derivatives show a high degree of diversity in molecular structure and cellular function. Individual content and composition of FFAs depend on a number of variables including the expression and activity of the enzymes involved in their anabolic or catabolic metabolism. This diversity of pathways for providing FFAs to the organism is thought to be of considerable importance. The intrinsic pathway describes the de novo FA synthesis (lipogenesis) from glucose, which is preferentially established in lipogenic tissues like liver and white adipose tissue. Intestinal absorption of dietary FFAs and their utilization by parenchymal organs are hallmarks of the extrinsic pathway. There are several links and crossing points between these two metabolic routes including sensing of FFAs with subsequent hormonal regulation of metabolism, FFA-dependent direct regulation of gene transcription, and
competitive modification of enzyme activities or gene expression by FFAs.

In cellular systems, structural changes to FFAs are important in the initiation of regulatory FFA effects. Inside cells, absorbed or de novo synthesized FFAs can be modified by several molecular mechanisms resulting in elongation, desaturation, peroxidation, and/or esterification. Synthesis of acyl-CoA derivatives is one important mechanism for solubilization of FFAs in an aqueous environment and for regulation of FFA distribution in cellular systems. Subsequently, FFAs and FFA derivatives are able to activate metabolite-sensitive transcription factors such as peroxisome proliferator-activated receptors (PPARs), Sterol Regulatory Element-binding Proteins (SREBPs), or FFA response elements.[1,2] In addition, it has been suggested that FFAs and their derivatives are able to act in a direct way without any cytoplasmic adapter molecule. Such mechanisms are utilized especially for FFA-dependent regulation of gene transcription.[3]

In multi-cellular organisms strong regulation and coordination of intrinsic and extrinsic metabolic FFA pathways are necessary to establish cellular synergy and to provide energy homeostasis. One important mechanism for achieving the balance between the two FFA pathway components is the sensing of FFAs entering the extrinsic metabolic pathway by several receptors and associated molecular structures.

Important molecules in FFA sensing structures belong to the family of G protein-coupled receptors (GPCRs). Aspects of their molecular structure, tissue expression pattern as well as their role in tissue homeostasis or disease are detailed below.

MOLECULAR STRUCTURE OF FFARs AND GPR120

GPCRs constitute one of the largest gene families yet identified with several hundred characterized receptors and more than hundred human genes encoding proteins probably belonging to this family, although the functional relevance and characteristics of a number of these receptors remain to be determined.[4] Consequently, these receptors with unknown function and ligands are referred to as orphan GPCRs and considered as a potentially fruitful source for drug discovery because a high proportion of all clinically available pharmaceuticals act on GPCRs. Unlike the monoamine or neuropeptide receptors, no clear GPCR homologs have so far been identified in invertebrates including Drosophila melanogaster or Caenorhabditis elegans, suggesting a relatively recent evolutionary origin.[5]

In recent decades several diverse strategies to characterize orphan GPCRs have been applied. These include PCR-based sequence alignments with well-defined receptors and the reverse pharmacology approach, which uses the cellular membranes of GPCR transfectants as targets to test the binding abilities of potential ligands. The low-stringency hybridization strategy has become the method of choice to detect subtypes of cloned GPCR.[6]

The deorphanizing strategy has successfully identified a cluster of four GPCR genes in close proximity to the CD22 gene on chromosome 19q13.1, poorly related to other GPCR subfamilies.[7] The genes downstream of CD22 named GPR40, GPR41, GPR42, and GPR43 (GPR40 family receptors) were further characterized with molecular techniques and function-related strategies. The four members of this subfamily share about 30% minimum sequence identity (Figure 1). However, GPR41 shows amino acid identity of 98% with GPR42. It has been suggested that high sequence homology between these two genes could be the result of a recent duplication event within a GPR42 pseudogene formation. In addition, expression of human GPR42 in yeast demonstrates that this receptor is not activated by carboxylic ligands.[8] Function-related mutagenesis studies have shown that amino acid 174 in extracellular loop 2 is of high importance for human GPCR signaling since conversion of the positively charged arginine 174 in GPR41 to tryptophan 174 as found in GPR42 (R174W) silences receptor activity (equivalent position in rat R170W). The single amino acid change R174W in GPR42 is sufficient to restore propionate responses.[9] Therefore, it is suggested that positively charged R174 is essential to form a salt bridge with carboxylate ligands in order to sense FFAs. The working hypothesis that GPR42 could be an inactive pseudogene has been recently rejected because the coded six amino acid difference, including amino acid 174, was identified as polymorphism.[10] Mutations in GPR42 are assumed to be responsible for diminishing its ability to respond to carboxylate ions. However, experimental data concerning GPR42 function and a putative crosstalk with GPR41 protein are not yet available. In humans, sequence analysis revealed an extensively diverged copy of GPR40 between the GPR41 and GPR42 genes indicating that the GPR42 generating duplication event has involved a DNA fragment that also contains GPR40. It has to be taken into account that, like GPR 40, the coding region of GPR40 family members lacks a typical intron-structure. Therefore, contaminating genomic DNA might give false positives in PCR-based expression analysis.

Transcription of GPR40 family members is under the control of several transcription factors. It has been recently shown that the transcription factor IPF1 (insulin promoter factor 1)/PDX1 (pancreatic duodenal homeobox-1) binds to an enhancer element within the 5'-flanking region of GPR40.[9] However, the IPF1/PDX1 activity on GPR40 varies in different regions of the gastrointestinal tract. A conserved and strong IPF1/PDX1 activity is probably restricted for GPR40 expression in cells of the gastric pylorus, duodenum, and pancreatic beta-cells.

The CD22 downstream GPCR genes are alternatively called free fatty acid receptor genes (FFARs) because their fundamental functional relevance in sensing of FFAs has been established.[11] Among the FFAR proteins ligand specificity differs remarkably. FFAR2 (GPR43) and FFAR3 (GPR41) are preferentially activated by short-chain FFAs (C2-C6), whereas sensing of medium- and long-chain FFAs (>C6) is processed by FFAR1 (GPR40). In addition to FFAR1,
Another medium- and long-chain FFA sensing GPCR termed GPR120 has been identified \cite{10,11}. In contrast to CD22-associated GPCR coding genes, the GPR120 gene is located on 10q23.33 and includes three exons. GPR120 is a member of the rhodopsin family of GPCRs with alternate splicing \cite{BC101175, NM_181745}. In humans, a functional significance is assumed for the GPR120 splice variants \cite{12}.

A summary of molecular and biochemical key features characterizing the discussed GPCRs is given in Table 1.

**INTESTINAL EXPRESSION PATTERN OF FFARs AND GPR120**

In the following, the term FFAR is preferentially used instead of GPR40, GPR41, and GPR43, because FFAR implicates a functional link and illustrates successful dephosphorylation which is not obvious from the term GPCR. In general, the intestinal mucosa is an important compartment for expression and synthesis of FFARs and GPR120\cite{13}. Mast cells are one lamina propria cell type expressing FFAR2 and FFAR3\cite{14}. This observation is highly important because pharmacological studies have shown that small-chain FFAs directly affect 5-HT and PYY release, probably mediated by FFARs.

In addition, FFARs and GPR120 are expressed in extra-intestinal tissues like adipose tissues, where high levels of FFAR3 and FFAR2 are found. GPR120 is also found in rat taste buds. Polymorphonuclear cells, i.e. neutrophils, are one important extra-intestinal location of FFAR2 expression, whereas FFAR1 is preferentially synthesized by pancreatic beta-cells. This tissue distribution indicates that the FFAR group members and GPR120 play critical roles in maintenance of physiological homeostasis in intestine-associated metabolic axes\cite{15}. In this context, intestinal and extra-intestinal cell types expressing FFARs or GPR120 are detailed below.

**FFAR1 (GPR40)**

As stated above, strong FFAR1 expression is found in...
Table 1 Molecular and biochemical characteristics of free fatty acid receptors and GPR120

| Receptor | Localization | Ligand | Signaling |
|----------|--------------|--------|-----------|
| FFAR1    | 19q13.1      | > C6: medium to long chain | Insulin, GLP-1, GIP |
| FFAR2    | 19q13.1      | C2-C6: acetate, propionate, butyrate | PYY, 5-HT |
| FFAR3    | 19q13.1      | C2-C6: propionate > butyrate > acetate | Leptin, PYY |
| GPR120   | 10q23.33     | Medium and long chain; alpha-linolenic acid, docosahexaenic acid, palmitoleic acid | GLP-1, CCK |

**FFAR**: free fatty acid receptor.

Table 2 Important cell types expressing free fatty acid receptors or GPR120

| FFAR1 | FFAR2 | FFAR3 | GPR120 |
|-------|-------|-------|--------|
| Enteronecric cells | ++ | +++ | + | ++ |
| Enteroctyes | (+) | (+) | + | + |
| Mast cells | + | + | + | + |
| Adipocytes | (+) | + | + | + |
| Neutrophiles | ++ | + | + | + |
| Eosinophiles | + | + | + | + |
| Beta-cells | +++ | + | + | + |
| Alpha-cells | + | + | + | + |

**FFAR**: free fatty acid receptor.

**FFAR2 (GPR43)**

In addition to extra-intestinal locations, FFAR2 is found in mucosal cells of the ileum and large intestine. The pattern and intensity of FFAR2 expression varies along the intestine and probably between species, which parallels the FFAR1 findings as detailed above. Important sources of FFAR2 synthesis are enteroendocrine cells, some types of lamina propria cells including mast cells, neutrophiles, eosinophiles and colonic epithelium. In enteronecric cells co-expression of FFAR2 with PYY is found, which is suggested as a FFAR2 function-related profile. However, coincidence of FFAR and PYY expression is additionally found for FFAR1. Paneth cells were constantly negative for FFAR2.

**FFAR3 (GPR41)**

In small and large intestinal mucosa, the FFAR3 expression pattern is similar to that of FFAR2. Intestinal FFAR3 tissue distribution is not homogenous and probably varies between species. Highest FFAR3 levels are found in the distal small intestine (ileum) and (proximal) colon. In such locations, FFAR3 is found in enteronecric cells and, occasionally, in the apical cytoplasm of surface lining enterocytes. Using anti-FFAR3 immunostaining, the protein is mainly detectable in Golgi apparatus and endoplasmic reticulum, but not in outer cellular membranes. In comparison with surface lining enterocytes, FFAR3 expression is weak in crypt lining epithelia. As stressed above, the FFAR3 protein is found abundantly in enteronecric cells, but the proportion of anti-FFAR3 immunostained enteronecric cells (about 0.01 cells/crypt) is less than for anti-FFAR2 stained cells (about 0.33 cells/crypt). At present, co-expression of FFAR2 and FFAR3 protein in enteronecric cells has not been demonstrated. Using a qRT-PCR approach, intraepithelial lymphocytes were found not to express appreciable levels of FFAR3. FFAR3 immunoreactive enteronecric cells are regularly positive for PYY, but not vice versa, and arenegative for 5-HT. FFAR3 is also localized to NeuroD- or Neurogenin3-producing enteronecric subpopulations. Experimental data are given which suggest FFAR3 protein modifications including N-linked glycosylation in the second extracellular loop (N160), one PKC site (S216), two combined PKA/PKC phosphorylation sites (T328, T329), and one palmitoylation site in the C-terminus (C295).

**GPR120**

Functional deorphanization has revealed the GPR120 protein as a receptor for FFAs with abundant expression in intestinal cells. Co-localization of GPR120 and GLP-1 in intraepithelial endocrine cells of intestinal mucosa, parti-
ccularly the colon, has been demonstrated by in situ hybridization experiments\[31\]. In duodenal and jejunal epithelia, GPR120 and FFAR1 mRNAs are expressed in GIP synthesizing K cells\[23\].

**FFARs AND GPR120 IN TISSUE**

**HOMEOSTASIS AND DISEASE**

The energy homeostasis/balance of vertebrates is strongly influenced by effective food digestion based on the synergy between the activity of enzymes encoded by the vertebrate genome and enzymes provided by the intestinal microbiome, a term describing the population of microbes that reside in the bowel. The synthesis of glycoside hydrodrolases, which are needed to digest complex dietary plant polysaccharides, is very limited in the intestinal mucosa, but a plethora of these enzymes is synthesized by the microbiome and supports digestion and absorption processes\[24\]. Complex dietary carbohydrates are processed by microbiome-encoded enzymes to short-chain FFAs, particularly acetate, propionate, and butyrate. In contrast to complex carbohydrates, the up-take of short-chain FFAs by the intestinal mucosa is very efficient and is achieved by passive diffusion and mono-carboxylic acid transporters. The most important roles of intestinal short-chain FFAs are as an energy source, in signaling, and in the induction of colonic motility\[19-22,27\]. Butyrate is adopted as the preferred energy source for colorectal enterocytes, whereas hepatocytes consume most of the absorbed propionate for gluconeogenesis. Acetate can be used as substrate in lipogenesis, a pathway primarily located in hepatocytes and adipocytes, but additionally found in colorectal enterocytes\[29\]. FFARs are expressed and synthesized by several intestinal cell types, and functional data argue for important roles of such receptors in nutrition regulation and energy homeostasis\[18,20\].

A paradigm in FFAR activation is coupling to inositol 1, 4, 5-triphosphate formation, intracellular Ca\(^{2+}\) release, ERK1/2 activation, and inhibition of cAMP accumulation. However, there is diversity among FFARs in coupling to G proteins which is of high importance for the regulation of associated pathways. For example, FFAR2 displays a dual coupling through Pertussis toxin-sensitive G\(_{i,8}\) family members and toxin-insensitive G\(_{s}\) proteins, whereas FFAR3 couples exclusively through G\(_{i,8}\)\[3\]. It has been shown that intracellular FFAR1 signaling is associated with G\(_{s}\) and phospholipase C as well as G\(_{i}\) coupling\[23\]. In FFARs, however, the long N-terminal extracellular domains that are characteristic of protease-activated receptors are not found, suggesting an aberrant mechanism of receptor activation\[1\].

The sensitivity of FFAR3 to short-chain FFAs declines from propionate to butyrate and acetate, whereas FFAR2 is equally sensitive to each short-chain FAA. However, acetate is more selective for FFAR2 than FFAR3. Long-chain FFAs are able to reduce ghrelin blood secretion, whereas cholecystokinin (CCK) levels are increased by medium- to long-chain FFAs\[29\].

**FFAR1 (GPR40)**

In order to study FFAR1 functions several strategies for creating transgenic or knockout mice have been adopted\[17\]. Transgenic mice characterized by a beta-cell specific overexpression of FFAR1 were normal at birth, but then developed glucose intolerance, followed by impaired first-phase insulin secretion and finally leading to diabetes. The pathophysiological findings were paralleled by an abnormal distribution pattern of alpha- and beta-cells within the islets of Langerhans and reduced insulin content. FFAR1-/- mice were healthy, fertile, and showed no distinctive metabolic phenotype under normal dietary conditions. On a high fat diet, however, knockout animals were more glucose tolerant than appropriate WT (+/+) animals. Both groups became equally obese, whereas knockout mice were more protected against hyperinsulinaemia, glucose-intolerance, and insulin-resistance\[28\].

It has been suggested that FFAR1 expression in enteroendocrine cells could indirectly stimulate the glucose-stimulated insulin secretion (GSIS) by pancreatic beta-cells through modulating the secretion of incretin hormones GIP and GLP-1 in response to FFAs provided in the gut lumen\[31\]. These findings have been further substantiated by experiments in FFAR1-/- mice demonstrating impaired secretion of both GIP and GLP-1 in response to oral dietary fat administration with a concomitant reduction in insulin secretion and glucose clearance\[34\]. The data suggest that FFAR1 is directly responsible for the acute stimulatory effects of fatty acids on GSIS and provide strong evidence for FFAR1 involvement in FFA-dependent stimulation of incretin secretion. At present, there is no functional evidence for FFAR1 activity in the secretory process of the gut hormones ghrelin (putative appetite hormone) and CCK (putative satiety hormone).

The FFAR1 experiments in mice demonstrate that the role of FFAR1 either as part of the beta-cell compensation for insulin resistance or in driving hyperinsulinaemia and liver insulin resistance/glucose intolerance depends on a tissue-specific FFAR1 expression level. In addition to intestinal mucosa, FFAR1 is expressed in rat omental adipose depots, but not in epididymal or perirenal depots, which may merit further studies of the possible functional role of omental adipose depots in the metabolic syndrome\[17,25,27\]. In summary, the functional data argue for FFAR1 as an attractive drug target for agonists or antagonists especially in treatment of diabetes type 2.

**FFAR2 (GPR43)**

FFAR2 is thought to have roles in immune cell function, hematopoiesis, and mast cell activity. Moreover, FFAR2 signaling has been correlated with an increase in adipogenesis\[33\]. As demonstrated in FFAR2-/- mice, lipolytic activity of adipocytes is diminished after acetate treatment and results in reduced plasma levels of free fatty acids\[33\]. These data argue for a potential role of FFAR2 in regulating plasma lipid profiles, including aspects of metabolic syndrome, and an interdependency with other FFARs such as FFAR1. In the intestine, phasic and tonic motility
might be attributable to the activation of short-chain fatty acid receptors. Among others, intestinal FFAR2 has been suggested as a candidate receptor in fatty acid sensing and regulation of colonic motility probably mediated by the release of PYY and subsequently 5-HT[14]. At present, an in-depth-analysis correlating intestinal FFAR2 expression and bowel disorders like irritable bowel syndrome or malnutrition is not available. However, it could be speculated that FFARs are involved in the complex 5-HT-associated pathogenesis as suggested for such diseases[15,16].

**FFAR3 (FFAR4)**

FFAR3 was shown to induce apoptosis via a p53/Bax pathway in an ischemia/reperfusion setting[10]. Using FFAR3 -/- mice it has been shown that the receptor is essential for microbiome-induced increases in host adiposity, implying a role in regulating leptin production[11]. In addition, the efficiency of caloric extraction from the diet depends principally on FFAR3 expression. PYY, another anorexigenic hormone, is also a regulator of gut motility characterized by dose-related inhibition of transit rate along the length of the gut[12]. In FFAR3 -/- mice, a microbiota-dependent increase in intestinal transit rate associated with higher cecal propionate and acetate concentrations has been recorded[13]. In such animals, reduced expression of fatty acid synthase in the liver was found, which was not attributable to alterations in hepatic expression of genes involved in long-chain fatty-acid transport, trafficking, or reesterification.

The FFAR3 system is probably not the first-line feedback system of the host to regulate microbiota colonization and species diversity. In FFAR3 -/- mice, levels of microbiotic colonization of the proximal colon were not significantly affected by receptor absence when compared to their WT (+/+ ) littermates[14]. However, bacterial colonization has the power to reduce FFAR1 mRNA expression, whereas FFAR3 absence does not affect FFAR1, FFAR2, and GPR120 expression.

**GPR120**

Physiological functions associated with intestinal GPR120 expression are related to GLP-1 release and CCK secretion. In mouse enterococciene STC-1 cultured cells, activation of GPR120 by alpha-linolenic acid, docosahexaenoic, or palmitoleic acid promotes GLP-1 secretion[15]. Initial experimental evidence indicates that (unsaturated long-chain) FFA-induced apoptosis inhibition is mediated through GPR120[16]. In addition, GPR120 has been suggested to mediate FFA-stimulated secretion of the GLP-1 from L-cells[17]. These ligand-dependent activities (medium- to long-chain FFAs) are similar to FFAR1 related functions despite the fact that human GPR120 shares only 10% amino acid identity with FFAR1[18]. In order to dissect GPR120- and FFAR1-related intestinal activities pharmacological strategies are being developed using GPR120-selective agonists like gliforin derivatives[19].

**CONCLUSION**

Intestinal FFA sensing is one important mechanism in multi-systemic communication. As an important source of FFARs and GPR120 expression and synthesis, enterococciene cells are strategically positioned for sensing and transducing information about the nutrient milieu of the gut and microbiome metabolic activity to the host. Intestinal receptor activities are determined by ligand specificity for FFAs and regulate total energy homeostasis and intestinal motility. FFAR1 and GPR120 signaling mediates the secretion of long-chain FFA-stimulated incretins, such as GLP-1. The release of PYY by short-chain FFAs is controlled by FFAR2 and FFAR3. From a pharmacological point of view, the development and characterization of drugs as well as probiotics modifying FFAR activities are of high interest.

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**REFERENCES**

1. Shimano H, SREBPc physiology and pathophysiology of the SREBP family. FEBS J 2009; 276: 616-621
2. Armoni M, Harel C, Bar-Yosef F, Milo S, Karnieli E. Free fatty acids repress the GLUT4 gene expression in cardiac muscle via novel response elements. J Biol Chem 2005; 280: 34786-34795
3. Duplus E, Forest C. Is there a single mechanism for fatty acid regulation of gene transcription? Biochem Pharmacol 2002; 64: 893-901
4. Le Poul E, Loison C, Struyf S, Springael JY, Lannoy V, Decobeeq ME, Brezillon S, Dupriez V, Vassart G, Van Damme J, Parmentier M, Deheus M. Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. J Biol Chem 2003; 278: 25481-25489
5. Brown AJ, Goldsworthy SM, Barnes AA, Eilert MM, Tcheang L, Daniels D, Muir AI, Wigglesworth MJ, Kinghorn I, Fraser NJ, Pike NB, Strum JC, Steplewski KM, Murdock PR, Holder JC, Marshall FH, Szerkeres PG, Wilson S, Ignar DM, Foord SM, Wise A, Dowell SJ. The Orphan G protein-coupled receptors FFAR4 and GPR43 are activated by propionate and other short chain carboxylic acids. J Biol Chem 2003; 278: 11312-11319
6. Chung S, Funakoshi T, Civelli O. Orphan GPCR research. Br J Pharmacol 2008; 153 Suppl 1: S339-S346
7. Sawzdargo M, George SR, Nguyen T, Xu S, Kolakowski LF, O'Dowd BF. A cluster of four novel human G protein-coupled receptor genes occurring in close proximity to CD22 gene on chromosome 19q13.1. Biochem Biophys Res Commun 1997; 239: 543-547
8. Liaw CW, Connolly DT. Sequence polymorphisms provide a common consensus sequence for GPR41 and GPR42. DNA Cell Biol 2009; 28: 555-560
9. Bartoo-Shiftman R, Ridner G, Bahar K, Rubins N, Walker MD. Regulation of the gene encoding GPR40, a fatty acid receptor expressed selectively in pancreatic beta cells. J Biol Chem 2007; 282: 22561-22571
10. Fredriksson R, Höglund PJ, Gloriam DE, Lagerström MC, Schiöth HB. Seven evolutionarily conserved human rhodopsin G protein-coupled receptors lacking close relatives. FEBS Lett 2003; 554: 381-388
11. Hirasawa A, Tsumaya K, Awaji T, Katsuma S, Adachi T, Yamada M, Sugimoto Y, Miyazaki S, Tsujimoto G. Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. Nat Med 2005; 11: 90-94

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Moore K, Zhang Q, Murgolo N, Hosted T, Duffy R. Cloning, expression, and pharmacological characterization of the GPR120 free fatty acid receptor from cynomolgus monkey: comparison with human GPR120 splice variants. *Comp Biochem Physiol B Biochem Mol Biol* 2009; 154: 419-426.

Miyachi S, Hirasawa A, Ichimura A, Hara T, Tsujimoto G. New frontiers in gut nutrient sensor research: free fatty acid sensing in the gastrointestinal tract. *J Pharmacol Sci* 2010; 112: 19-24.

Tazoe H, Otomo Y, Kaji I, Tanaka R, Karaki SI, Kujwahara A. Roles of short-chain fatty acids receptors, GPR41 and GPR43 on colonic functions. *J Physiol Pharmacol* 2008; 59 Suppl 2: 251-262.

Ichimura A, Hirasawa A, Hara T, Tsujimoto G. Free fatty acid receptors act as nutrient sensors to regulate energy homeostasis. *Prostaglandins Other Lipid Mediat* 2009; 89: 82-88.

Edfalk S, Stoneberg P, Edlund H. Gpr40 is expressed in enteroendocrine cells and mediates free fatty acid stimulation of incretin secretion. *Diabetes* 2008; 57: 2280-2287.

Brownlie R, Mayers RM, Pierce JA, Marley AE, Smith DM. The long-chain fatty acid receptor, GPR40, and glucolipotoxicity: investigations using GPR40-knockout mice. *Biochem Soc Trans* 2008; 36: 950-954.

Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F, Arts D, Xavier RJ, Teixeira MM, Mackay CR. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature* 2009; 461: 1282-1286.

Karaki S, Tazoe H, Hayashi H, Kashiwabara H, Tsyuyama K, Suzuki Y, Kujwahara A. Expression of the short-chain fatty acid receptor, GPR43, in the human colon. *J Mol Histol* 2008; 39: 135-142.

Karaki S, Mitsui R, Hayashi H, Kato I, Sugiya H, Iwanaga T, Furness JB, Kujwahara A. Short-chain fatty acid receptor, GPR43, is expressed by enteroendocrine cells and mucosal mast cells in rat intestine. *Cell Tissue Res* 2006; 324: 353-360.

Tazoe H, Otomo Y, Karaki S, Kato I, Fukami Y, Terasaki M, Kujwahara A. Expression of short-chain fatty acid receptor GPR41 in the human colon. *Biomed Res* 2009; 30: 149-156.

Samuel BS, Shaito A, Motoike T, Roy FE, Backhed F, Manchester JK, Hamer RE, Williams SC, Crowley J, Nagasawa M, Gordon JI. Effects of the gut microbiota on host adiposity are modulated by the short-chain fatty-acid binding G protein-coupled receptor, Gpr41. *Proc Natl Acad Sci USA* 2008; 105: 16767-16772.

Parker HE, Habib AM, Rogers GJ, Gribble FM, Reimann F. Nutrient-dependent secretion of glucose-dependent insulino-motric polypeptide from primary murine K cells. *Diabetologia* 2009; 52: 289-298.

Bäckhed F, Crawford PA. Coordinated regulation of the metabolome and lipidome at the host-microbial interface. *Biochim Biophys Acta* 2010; 1801: 240-245.

Musso G, Gambino R, Cassader M. Gut microbiota as a regulator of energy homeostasis and ectopic fat deposition: mechanisms and implications for metabolic disorders. *Curr Opin Lipidol* 2010; 21: 76-83.

de La Serre CB, Ellis CL, Lee J, Hartman AL, Rutledge JC, Rayould HE. Propensity to high-fat diet-induced obesity in rats is associated with changes in the gut microbiota and gut inflammation. *Am J Physiol Gastrointest Liver Physiol* 2010; 299: G440-G448.

Musso G, Gambino R, Cassader M. Obesity, diabetes, and gut microbiota: the hygiene hypothesis expanded? *Diabetes Care* 2010; 33: 2277-2284.

Mellitzer G, Beucher A, Lobstein V, Michel P, Robine S, Heding M, Gradwohl G. Loss of enteroendocrine cells in mice alters lipid absorption and glucose homeostasis and impairs postnataal survival. *J Clin Invest* 2010; 120: 1708-1721.

Feinle-Bisset C, Patterson M, Gheati MA, Bloom SR, Horowitz M. Fat digestion is required for suppression of ghrelin and stimulation of peptide YY and pancreatic polypeptide secretion by intraduodenal lipid. *Am J Physiol Endocrinol Metab* 2005; 289: E948-E953.

Latour MG, Alquier T, Oseid E, Tremblay C, Jetton TL, Luo J, Lin DC, Poitout V. GPR40 is necessary but not sufficient for fatty acid stimulation of insulin secretion in vivo. *Diabetes* 2007; 56: 1087-1094.

Yamada Y, Miyawaki K, Tsukiyama K, Harada N, Yamada C, Seino Y. Pancreatic and extrapancreatic effects of gastric inhibitory polypeptide. *Diabetes* 2006; 55: S86-S91.

Hong YH, Nishimura Y, Hishikawa D, Tsuzuki H, Miyahara H, Gotoh C, Choi KC, Feng DD, Chen C, Lee HG, Katoh K, Roh SG, Sasaki S. Acetate and propionate short chain fatty acids stimulate adipogenesis via GPR43. *Endocrinology* 2005; 146: 5092-5100.

Ge H, Li X, Weizsamm J, Wang P, Barbiault H, Chen JL, Tian H, Li Y. Activation of G protein-coupled receptor 43 in adipocytes leads to inhibition of lipolysis and suppression of plasma free fatty acids. *Endocrinology* 2008; 149: 4519-2456.

Niesler B, Kapeller J, Fell C, Atkinson W, Möller D, Fischer C, Wohrwe P, Houghton LA. 5-HTTLPR and SINT2 polymorphisms in the serotonin transporter gene and irritable bowel syndrome: effect of bowel habit and sex. *Eur J Gastroenterol Hepatol* 2010; 22: 856-861.

Hammer C, Kapeller J, Endele M, Fischer C, Hebebrand J, Hinney A, Friedel S, Graçaos M, Estivill X, Fichter M, Fernández-Araña F, Ehrlich S, Rappold G, Niesler B. Functional variants of the serotonin receptor type 5A and B gene are associated with eating disorders. *Pharmacogenet Genomics* 2009; 19: 790-799.

Kimura M, Mizukami Y, Miura T, Fujimoto K, Kobayashi S, Matsuzaki M, Orphan G. Protein-coupled receptor, GPR41, induces apoptosis via a p53/Bax pathway during ischemic hypoxia and reoxygenation. *J Biol Chem* 2001; 276: 26453-26460.

Lin HC, Neevel C, Chen JH. Slowing intestinal transit by PPY depends on serotonergic and opioid pathways. *Am J Physiol Gastrointest Liver Physiol* 2004; 286: G558-G563.

Katsuma S, Hatae N, Yano T, Ruike Y, Kimura M, Hirasawa A, Tsujimoto G. Free fatty acids inhibit serum deprivation-induced apoptosis through GPR120 in a murine enteroendocrine cell line STC-1. *J Biol Chem* 2005; 280: 19507-19515.

Hara T, Hirasawa A, Sun Q, Sadakane K, Itsubo C, Iga T, Adachi T, Koshimizu TA, Hashimoto T, Asakawa Y, Tsujimoto G. Novel selective ligands for free fatty acid receptors GPR120 and GPR40. *Naunyn Schmiedebergs Arch Pharmacol* 2009; 380: 247-255.

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