Appendix 1

Title	Author	Year	Model	Method	Key Findings
Microbial Fermentation Of Flaxseed Fibres Modulates The Transcriptome Of GPR41-Expressing Enteroendocrine Cells And Protects Mice Against Diet-Induced Obesity.	Arora, Tulika Rudenko, Olga Egerod, Kristoffer Lihme Husted, Anna Sofie Kovatcheva-Datchary, Petia Akrami, Rozita Kristensen, Mette Schwartz, Thue W Bäckhed, Fredrik	2018	Mouse	GPR41 promoter controlled red fluorescent protein in mice fed 4 different diets: normal chow, high fat diet, high fat diet with 10% non-fermentable fibre cellulose and high fat diet with 10% fermentable flaxseed fiber. All diets were conducted for 12 weeks. Evaluation of: microbiota changes enteroendocrine cell transcriptome in ileum and colon. Additionally, the authors measured body weight and fat mass, energy expenditure, food and water intake during exercise. SCFAs and organic acids were measured by gas chromatography. GPR41 controlled RFP mice. Randomly assigned to the aforementioned 4 diets. The ileum and colon tissue was harvested, used to create a single cell suspension for RNA extraction to evaluate the transcriptome.	Supplementation of flaxseed fibres increases the abundance of caecal *Akkermansia* and *Bifidobacterium.* A high fat with the addition of flaxseed fibre restored butyrate level to comparable of that in mice fed normal chow. Measurements of acetate and propionate were unaffected by soluble fibre. Flaxseed supplementation alters GPR41 expression.

The Microbiome Of Professional Athletes Differs From That Of More Sedentary Subjects In Composition And Particularly At The Functional Metabolic Level	Barton, Wiley Penney, Nicholas C Cronin, Owen Garcia-Perez, Isabel Molloy, Michael G Holmes, Elaine Shanahan, Fergus Cotter, Paul D O'Sullivan, Orla	2018	Human	Metabolic phenotyping and metagenomic analysis of the gut microbiome of 40 professional international rugby union players. Whole metagenome shotgun sequencing, metabolic phenotype of the players and the gut microbiota.	Diversity of microbiota increased in professional athletes compared with high BMI and low BMI controls. Increased Akkermansia in the gut of the athlete population. Difference of 98 metabolic pathways between athlete and control cohorts. The athlete group had the highest mean difference in metabolic pathways. The SCFA levels in faecal matter showed significantly higher levels of acetate relative to control samples.

Microbiota-Generated Metabolites Promote Metabolic Benefits Via Gut-Brain Neural Circuits.	De Vadder, Filipe Kovatcheva-Datchary, Petia Goncalves, Daisy Vinera, Jennifer Zitoun, Carine Duchampt, Adeline Bäckhed, Fredrik Mithieux, Gilles	2014	Rat	Measurement of gluconeogenesis in rats fed propionate, butyrate and fructo-oligosaccharides. Model of Caco-2 cells for intestinal enterocytes, exposed to butyrate to measure G6PC and PCK1 expression as well as intracellular cAMP concentration. Assessment of whether propionate mediates intestinal gluconeogenesis through gut-brain communication through periportal nervous deafferation. Rat models were fed SCFA and fructo-oligosacharide diets for 2 weeks. Immunofluorescence was conducted to identify FFAR3 expression in the portal vein. Exposure to beta hydroxybutyrate, an antagonist for GPR41 to identify whether this affected propionate-induced GPR41 activation.	Propionate and butyrate activate intestinal gluconeogenesis. Propionate-induced gluconeogenesis accounted for 23% of total glucose production. In vitro exposure to butyrate resulted in G6PC and PCK1 expression as well as a 3 fold increase of intracellular cAMP Propionate induces IGN gene expression via a gut-brain neural circuit. Propionate could not increase G6Pase activity and PCK1, but butyrate could. Propionate activation can be reversed by Beta-hydroxybutyrate. Dietary propionate causes a 2 to 3-fold increase in the expression of c-Fos. Neuronal activation was not seen in capsaicin- treated rats.

The Gut Microbiota Suppresses Insulin-Mediated Fat Accumulation Via The Short-Chain Fatty Acid Receptor GPR43.	Kimura, Ikuo Ozawa, Kentaro Inoue, Daisuke Imamura, Takeshi Kimura, Kumi Maeda, Takeshi Terasawa, Kazuya Kashihara, Daiji Hirano, Kanako Tani, Taeko Takahashi, Tomoyuki Miyauchi, Satoshi Shioi, Go Inoue, Hiroshi Tsujimoto, Gozoh	2013	Mouse	P2 promoter-driven adipose-specific Gpr43 transgenic mice. Exposure with acetate followed by bolus of insulin was administered intraperitoneally. Measurement of Akt phosphorylation of Ser473. Evaluation of SCFA and GPR43 activity on insulin signalling in white adipose tissue.	Differences in acetate-supressed insulin impact were seen in distinct mouse and tissue. Lipoprotein lipase activity was higher in GPR43 knockout mice and lower in the Ap2-promoter driven transgenic mice. Acetate supressed insulin-induced glucose and fatty acid uptake in adipocytes, not in Gpr43 knockout mice. Plasma triglycerides were low in Gpr43 knockout mice fed high fat diets when compared with aP2-GPR43 transgenic mouse. This effect was not demonstrated in germ- free mice or after antibiotics, indicating a role of the gut microbiota. GPR43 promotes energy expenditure through uptake of glucose and lipids into other tissues other than adipose.

ANGPTL4 Expression Induced By Butyrate And Rosiglitazone In Human Intestinal Epithelial Cells Utilizes Independent Pathways.	Korecka, Agata de Wouters, Tomas Cultrone, Antonietta Lapaque, Nicolas Pettersson, Sven Doré, Joël Blottière, Hervé M Arulampalam, Velmurugesan	2013	Cell Model + mouse model	Using cell lines, exposed to butyrate or rosiglitazone. This was repeated in HT-29 cells - as this showed largest initial response. Butyrate administration to germ-free mice, comparison with sterile water as a control. Measured ANGPLT4 mRNA expression in epithelial cells. Measured PPAR-γ in HT-29 cells treated with butyrate acetate and proprionate. Introduction of *C. tyrobutyricum* to germ-free mice. Measured induction of ANGPTL4 expression in ileal and colonic epithelium samples.	All 3 cell lines showed an increase in ANGPTL4 transcription when exposed to butyrate. When treating the cells with butyrate, the level of PPAR-γ was lower. Butyrate-induced ANGPLT4 expression is not dependent on PPAR-γ signalling.
Microbial Modulation Of Energy Availability In The Colon Regulates Intestinal Transit.	Wichmann, Anita Allahyar, Ava Greiner, Thomas U Plovier, Hubert Lundén, Gunnel Östergren Larsson, Thomas Drucker, Daniel J Delzenne, Nathalie M Cani, Patrice D Bäckhed, Fredrik	2013	Mice	The authors compared portal vein expression of GLP-1 in germ-free mice to wild type mice. Transplanted microbiota from a wild type mouse and measured Gcg expression in the colon after 24 and 72 hr. Incubation of proximal colon tissue with either a physiological concentration of SCFAs or saline as a control.	The absence of microbially-produced SCFAs in germ-free mice colon results in significantly higher plasma GLP-1 levels compared with germ free control mice. After 72 hours the number of GLP-1 expressing cells decreased to baseline levels. Colonic tissue when exposed to SCFAs showed reduction in Gcg expression in GF colon.

Activation Of Short And Long Chain Fatty Acid Sensing Machinery In The Ileum Lowers Glucose Production In Vivo.	Zadeh-Tahmasebi, Melika Duca, Frank A Rasmussen, Brittany A Bauer, Paige V Côté, Clémence D Filippi, Beatrice M Lam, Tony K T	2016	Rat	Propionate infusion into ileum whilst using pancreatic clamping to maintain plasma glucose measurements. They used viral knockdown of FFAR2. Then compared to GLP-1 antagonist and repeated experiment. Additionally authors used local anaesthetic infusion to limit influence of gut vagal afferents.	In wild type mice, propionate infusion for 50 minutes resulted in an increase in glucose needed to maintain euglycemia. Ileal infusion with propionate resulted in an increase glucose demand to maintain euglycemia. These effects were not seen with plasma infusion. Propionate sensing is dependent on the activation of FFAR2.