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Review article

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Gut microbiota in overweight and obesity: crosstalk with adipose tissue

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Abstract

Overweight and obesity are characterized by excessive fat mass accumulation produced when energy intake exceeds energy expenditure. One plausible way to control energy expenditure is to modulate thermogenic pathways in white adipose tissue (WAT) and/or brown adipose tissue (BAT). Among the different environmental factors capable of influencing host metabolism and energy balance, the gut microbiota is now considered a key player. Following pioneering studies showing that mice lacking gut microbes (that is, germ-free mice) or depleted of their gut microbiota (that is, using antibiotics) developed less adipose tissue, numerous studies have investigated the complex interactions existing between gut bacteria, some of their membrane components (that is, lipopolysaccharides), and their metabolites (that is, short-chain fatty acids, endocannabinoids, bile acids, aryl hydrocarbon receptor ligands and tryptophan derivatives) as well as their contribution to the browning and/or beiging of WAT and changes in BAT activity. In this Review, we discuss the general physiology of both WAT and BAT. Subsequently, we introduce how gut bacteria and different microbiota-derived metabolites, their receptors and signalling pathways can regulate the development of adipose tissue and its metabolic capacities. Finally, we describe the key challenges in moving from bench to bedside by presenting specific key examples.

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Key points

- Approximately 40% of the global population is affected by overweight or obesity; novel treatments focusing on modulating thermogenic pathways in adipose tissue and altering gut microbiota are being explored.
- Adipose tissues, categorized as white, brown and beige, have distinct roles in energy storage, thermogenesis and metabolism in the body.
- Environmental factors substantially influence energy metabolism, with diet, exercise and sleep being primary contributors.
- Gut bacteria are involved in bidirectional communication between the gut and adipose tissue, influencing energy metabolism, nutrient absorption, appetite and adipose tissue function.
- Adipose tissue hosts its own distinct microbiota, which varies based on metabolic health and other factors; its understanding could offer novel insights.
- Translating gut microbiota research from animal models to human applications faces methodological and biological challenges.

Introduction

Today, approximately 2.6 billion people globally — roughly 40% of the population in the world — are affected by overweight or obesity. Unless drastic and decisive actions are taken to curb this growing epidemic, it is estimated that more than 4 billion people (half of the population in the world) will be affected by overweight or obesity by 2035 (research by the World Obesity Federation).

Overweight and obesity are characterized by an excessive accumulation of fat (adipose) mass, which results from an imbalance between energy intake (calories consumed through food and beverages) and energy expenditure (calories burned through metabolic processes). Excessive calorie intake and a sedentary lifestyle are considered the primary factors contributing to the development of overweight and obesity — the underlying causes are complex and multifactorial and can be influenced by genetic, environmental and behavioural factors.

Obesity is associated with several adverse health consequences, including metabolic disorders such as type 2 diabetes, cardiovascular disease and certain types of cancer[1,2]. Therefore, novel therapeutic strategies are urgently needed to address the increasing prevalence of obesity and its associated health problems. One promising approach is the modulation of thermogenic pathways in white adipose tissue (WAT) and brown adipose tissue (BAT), which can help control energy expenditure and contribute to weight loss (Fig. 1). Additionally, the gut microbiota has emerged as a key player in regulating host metabolism and energy balance, and its modulation through targeted approaches might hold promise for the treatment of overweight and obesity[3,4]. In this Review, we first provide a general overview of adipose tissues and highlight the distinctions between humans and mice, the most commonly used animal model for the study of obesity and associated comorbidities. Subsequently, we delve into a comprehensive examination of the intricate mechanisms linking the gut microbiota and adipose tissue metabolism.

Types of adipose tissue

For a long time, adipose tissue was thought to be simply a passive storage site for excess energy in the form of fat. However, research has revealed that it is an active and dynamic endocrine organ that secretes hormones and has a crucial role in regulating metabolism and other physiological processes in the body (for a historical perspective, see ref. 5). Adipose tissues in the human body can be divided based on their location (subcutaneous and visceral) or based on their morphology (WAT or BAT), and each depot has its own unique physiological and metabolic characteristics (Box 1 and Fig. 2). It has been suggested that, when subcutaneous adipose tissue (SAT) expansion is impaired, especially when hyperplasia is restricted, it leads to ectopic fat deposition in the liver and skeletal muscle, contributing to the pathogenesis of obesity-related disorders[6–8]. Sustained metabolic alterations might drive changes from healthy to dysfunctional adipose tissues that can have systemic consequences[9–11]. Although excess visceral fat correlates with both metabolic and cardiovascular risk factors, expansion of subcutaneous fat in humans is associated with neutral or beneficial effects on metabolism[12,13]. There is a growing recognition that subcutaneous adiposity might have a protective role in metabolism[14,15]. In line with this, human trials have revealed that large-volume liposuction of subcutaneous WAT offers minimal to no metabolic advantages[16]. Evidence from mouse models has further suggested that transplanting subcutaneous WAT into the visceral cavity of recipient mice led to decreased body weight, total fat mass, glucose, and insulin levels and improved insulin sensitivity, whereas transplanted visceral fat had no effect[17]. These data suggest that subcutaneous fat is intrinsically different from visceral fat.

White adipose tissue

WAT is the most abundant type of adipose tissue in the body and is responsible for storing excess energy in the form of triglycerides. WAT is composed of adipocytes, which are specialized cells that can store and release lipids depending on the energy needs of the body. In addition to adipocytes, WAT contains stromal cells, immune cells and extracellular matrix components[18].

WAT is primarily located in subcutaneous and visceral depots, with the latter being more strongly associated with metabolic dysfunction and disease[18]. Subcutaneous WAT is located beneath the skin and is more metabolically active than visceral WAT (VAT), whereas VAT is located around internal organs and is more associated with insulin resistance and other metabolic disorders[18] (Fig. 3).

Within these adipose tissue categories (VAT and subcutaneous WAT), there are several subtypes of depots. VAT includes epicardial adipose tissue, perirenal adipose tissue, retroperitoneal adipose tissue and mesenteric adipose tissue located along the gastrointestinal tract. These depots have different anatomical locations, cellular characteristics, metabolic functions and health implications[19,20]. For example, adipose tissue surrounding the kidneys acts primarily as a cushion and thermal insulator. It also influences renal function and blood pressure regulation by secreting adipokines and pro-inflammatory cytokines. The mesenteric adipose tissue, on the other hand, has a role in intestinal immunity, barrier function and nutrient absorption[21,22]. It also modulates gut motility, secretion and hormone release by interacting with the enteric nervous system and the gut microbiota[23].

Brown adipose tissue

BAT is less abundant than WAT, primarily located in the supraclavicular and interscapular regions of the body, and its distribution is

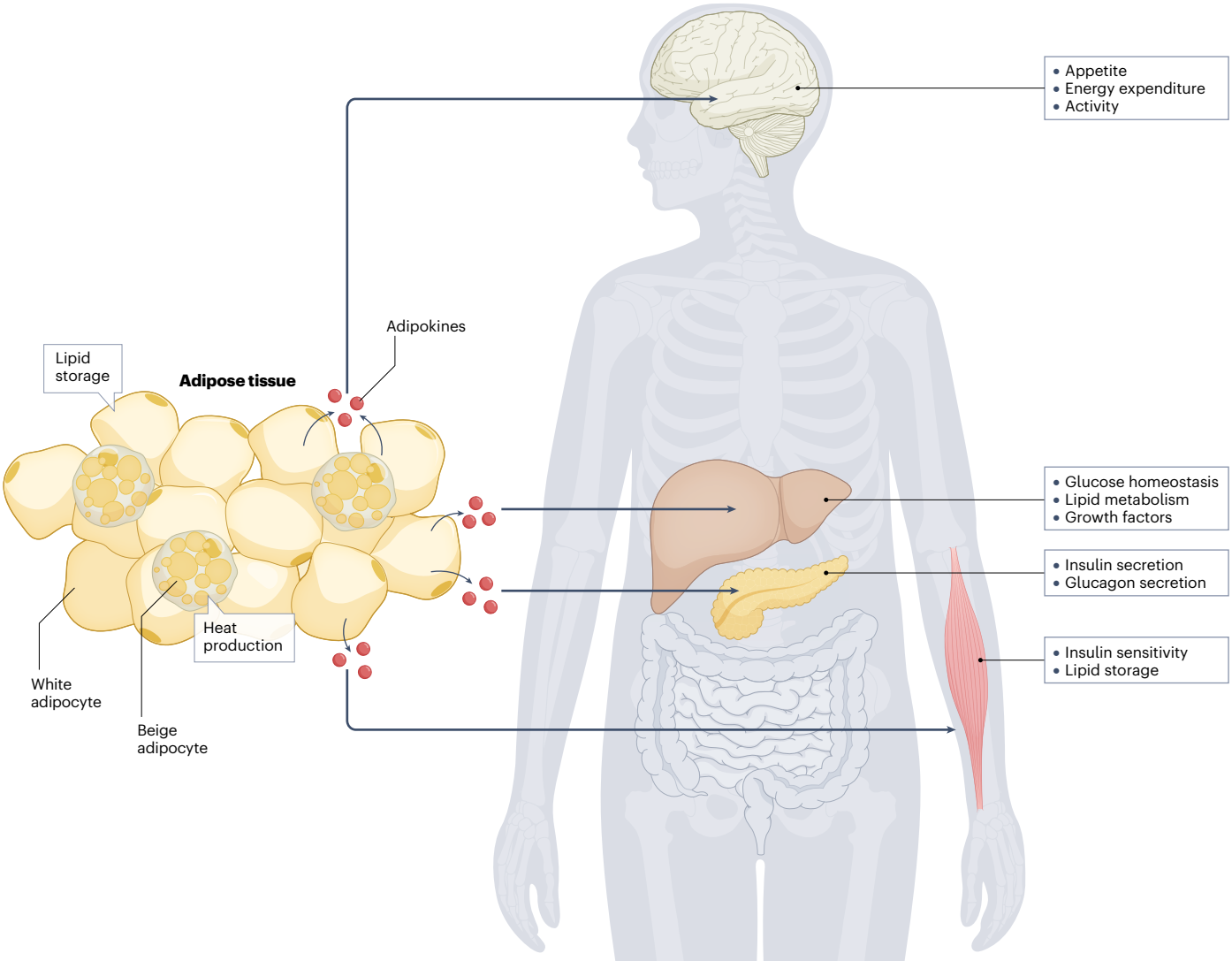


Fig. 1 | Effect of adipose tissues and adipokines on peripheral tissues and metabolism. Besides storing lipids (white and beige adipose tissue) and producing heat (beige and brown adipose tissue), adipose tissue in humans participates in various metabolic functions through the production of adipokines. A representation of the main peripheral target organs and the physiological process involved is depicted.

highly variable between individuals[24] (Fig. 3). It comprises multilocular adipocytes that contain numerous cytoplasmic lipid droplets with a central nucleus and a very large number of mitochondria, giving them their characteristic brown colour[25]. This specialized type of adipose tissue is responsible for producing heat by burning stored lipids through a process called non-shivering thermogenesis. This process is achieved through high expression of uncoupling protein 1 (UCP1), a protein of the inner mitochondrial membrane responsible for the uncoupling of respiration and thermogenic activity[25]. BAT is more metabolically active than WAT and has been shown to have a role in regulating energy homeostasis and glucose metabolism (Fig. 2). In addition, BAT has also been shown to secrete various cytokines and other factors that can influence systemic metabolism[25–27]. Brown adipocytes might share a common origin with skeletal muscle cells in the form of MYF5-expressing progenitor cells[28–30]. However, as shown in mice, MYF5 precursors are not the exclusive source of brown adipocytes, and they might also contribute to the mature white and beige adipocyte populations[31]. In addition, inducible non-MYF5-expressing progenitors of brown adipocytes have also been found in WAT depots and between muscle bundles in mice[32]. In 2023, two complementary papers demonstrated that adipose progenitors from different human fat depots, including BAT and WAT, shared similar transcriptomes, indicating a common progenitor. These progenitors differentiated into one of two main cell fates: adipogenic cells or multipotent cells called structural WNT-regulated adipose tissue-resident (SWAT) cells[33,34], providing a pool of progenitors that is maintained throughout life. The researchers suggested that the delicate balance between those two cell fates – differentiated adipocytes and undifferentiated, multipotent progenitors – might be a determining factor in adipose tissue composition and function.

Beige adipose tissue

Beige adipose tissue (sometimes referred to as brite adipose tissue) is a type of adipose tissue that is intermediate between WAT and BAT. Beige adipose tissue is found within some WAT depots and shares morphological and functional features of BAT such as the ability to burn stored lipids and produce heat[25] (Fig. 2). The possibility that thermogenesis can be induced within adipose tissue to regulate energy homeostasis and combat the development of obesity has led to high interest in the identification of so-called browning agents (that is, conditions or agents that can increase the amount or activity of UCP1 in adipose tissues)[35]. Despite promising results in animal (mouse and rat) studies showing that beige adipocytes can be induced in response to various stimuli, including cold exposure, exercise and certain pharmacological agents, the pathophysiological relevance of this remains unclear, as the thermogenic capacity associated with beige browning is probably only of secondary physiological importance compared to that of classical BAT[35]. Indeed, in mice, the amount of UCP1 expressed by beige adipocytes is less than 10% of that expressed by brown adipocytes[36], and the physiological effects might be disproportionately ascribed to beige tissues because most experiments in mice are still conducted below thermoneutral temperatures, which is the range of temperatures in which an animal does not need to regulate its body temperature. In contrast, adult humans usually live in thermoneutral conditions, so they might not activate their beige adipose tissue as much as mice do in these studies[36] (Figs. 2 and 3).

Environmental factors affecting energy metabolism

Energy metabolism is a complex process that involves converting food into energy forms usable by the body. The accurate regulation of energy metabolism is critical for maintaining energy balance and preventing the development of obesity and associated metabolic disorders. Although intrinsic biological factors, such as age, sex and genetics, certainly have a role in energy metabolism, environmental factors, including diet, exercise and sleep, also have a substantial effect[37] (Fig. 4). Finally, it is worth noting that the gut microbiota can also have a role in regulating adipose tissue metabolism and thermogenesis and the composition and function of the gut microbiota can differ between humans and mice[38]. These differences highlight the importance of studying both human and mouse models to fully understand the role of adipose tissue in metabolic health and disease.

Diet

Diet is one of the most important environmental factors affecting energy metabolism. Besides the number of calories consumed, research has shown that the quality of the diet can markedly affect energy intake, energy expenditure and energy metabolism[39,40].

Energy intake is affected by the quality of the diet in several ways. For example, foods high in fibre and protein tend to be more filling and can reduce overall calorie intake. In contrast, highly processed and energy-dense foods are often less satiating and can lead to overconsumption. Additionally, the source of calories can affect appetite and food choices, with some studies suggesting that high-fat diets might increase hunger and promote the consumption of calorie-dense foods[41].

The quality of the diet can also influence energy expenditure. Physical activity and exercise are important factors in energy expenditure but the thermic effect of food (TEF) also contributes to about 10% of the total energy expenditure[42,43]. TEF is the energy required to digest, absorb and metabolize food; it varies between individuals[44] and depends on the levels of physical activity and the macronutrient

Box 1

Key differences between human and mouse adipose tissues[245,246]

- Mouse and human white adipose tissue (WAT) is divided into two major anatomical regions — subcutaneous and visceral fat — but the distribution can be different between species.
- Mouse (white) subcutaneous fat is primarily located in the posterior inguinal and the anterior axillary region.
- Human subcutaneous fat develops in the abdominal region and the femoral and gluteal regions, especially in women[245].
- Human abdominal subcutaneous adipose tissue consists of two individual layers — the superficial layer and deep adipose tissue — separated by the fascia of Scarpa, whereas mice lack this anatomical division[245].
- Human omental WAT is the major visceral depot, whereas, in mice, this is the perigonadal WAT (also referred to as epididymal fat in males and periovarian fat in females), which humans almost completely lack.
- Some depots that are physiologically important in humans are not commonly present in lean, adult mice and only become apparent after induction of obesity[247]. This is the case for mesenteric and omental visceral WAT, and their effect on mouse systemic metabolism might be limited[248].
- Although most researchers agree that mouse inguinal WAT and human abdominal WAT are comparable, this is not the case for mouse perigonadal WAT and human omental WAT, which differ in location, function and draining circulation, and eventually have distinct physiological roles[249–251]. In mice, mesenteric fat is likely the most comparable visceral adipose tissue. 'True' visceral depots are omental and mesenteric as they are fat drained by the portal vein, whereas intra-abdominal depots are drained by the inferior vena cava, including perigonadal, retroperitoneal and perirenal fat.
- Hypertrophy and hyperplasia are two mechanisms by which adipose tissue can grow. Hypertrophy refers to an increase in the size of existing adipocytes, whereas hyperplasia refers to an increase in the number of adipocytes through the proliferation and differentiation of preadipocytes. Hypertrophy and hyperplasia can occur in humans and mice; hypertrophy is believed to be the primary mechanism by which adipose tissue grows in humans, whereas hyperplasia occurs more often in mice. Hypertrophic cells are considered less metabolically favourable and are associated with pathophysiological conditions[252].
- Mice have higher levels of brown and beige adipose tissue than humans, which might contribute to their increased metabolic rate and resistance to obesity[253].

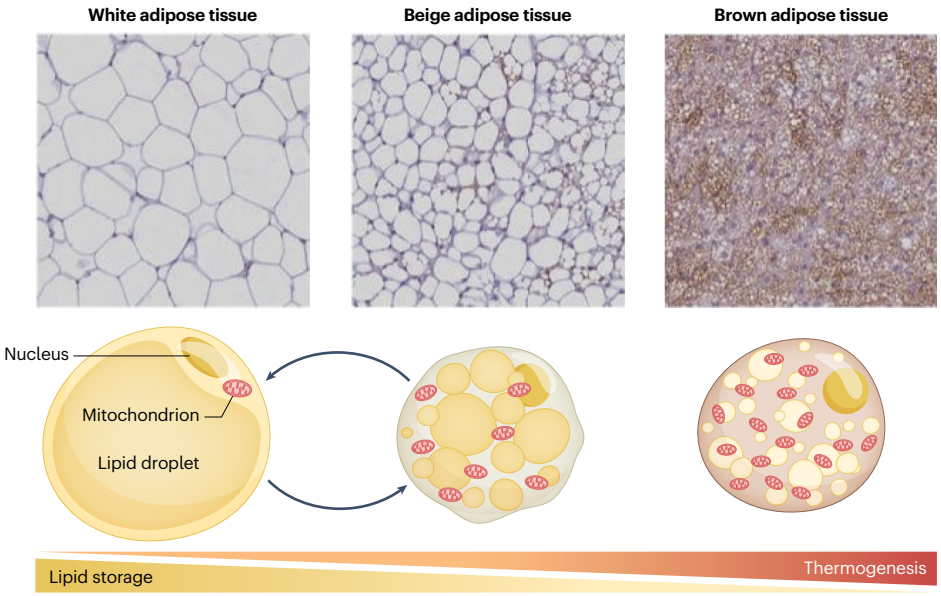
composition of the diet[43,45]. Protein has a higher TEF than carbohydrates or fats, meaning a high-protein diet might increase energy expenditure compared to a low-protein diet[43,46].

Diet composition can also affect energy metabolism. Diets high in sugar and refined carbohydrates have been linked to insulin resistance and impaired glucose metabolism, affecting the ability of the body to use energy efficiently[47]. In contrast, diets rich in fibres, whole grains, fruits and vegetables can improve insulin sensitivity and promote more efficient energy use[48–50].

Exercise

Exercise can increase energy expenditure and improve metabolic health by promoting the development of lean muscle mass, improving insulin sensitivity and reducing inflammation[51]. In addition, exercise can increase the expression of genes involved in energy metabolism. One important pathway is the AMP-activated protein kinase (AMPK) pathway, which is activated during exercise and increases glucose uptake and fatty acid oxidation in muscle cells[52]. AMPK also regulates mitochondrial biogenesis and oxidative metabolism, improving energy metabolism and metabolic health[52]. Another crucial pathway is the peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α) pathway, which is involved in mitochondrial biogenesis and oxidative metabolism. Exercise has been shown to increase PGC1α expression, leading to increased mitochondrial biogenesis and improved energy metabolism[53].

It has been shown that exercise could directly influence the production of specific bioactive lipids from the BAT. The release of substances from this tissue during exercise has been suggested as a possible mechanism for some health benefits associated with regular physical activity. Through lipidomic analysis, researchers found that a session of moderate-intensity exercise significantly ($P < 0.05$) raises the levels of a circulating linoleic acid metabolite called 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME) in individuals of various demographics, including men, women, young (age 24–42 years) and older (age 65–90 years) individuals, as well as those who are physically active or follow a sedentary lifestyle[54]. 12,13-DiHOME, a BAT-derived metabolite (batokine), is also released in response to cold[55]. However, in the context of exercise, studies conducted in mice have shown that both a single exercise session and regular exercise training increase the levels of circulating 12,13-diHOME directly from BAT[54]. If BAT is surgically removed, this increase in 12,13-diHOME is abolished. Furthermore, administering 12,13-diHOME to mice resulted in enhanced uptake and



	White adipose tissue	Beige adipose tissue	Brown adipose tissue
Morphology	Large, spherical cell with a large, unilocular fat droplet and a flattened peripheral nucleus	Smaller, elliptical cell with multilocular fat droplets	Small, elliptical cell with multilocular fat droplets with an oval central nucleus
Primary function	Energy storage	Energy storage and thermogenic potential	Thermogenesis
UCP1 expression	Undetectable	Positive	Positive
Mitochondrial density	Low	Medium	High
Heat production	–	+	+++

Fig. 2 | Different types of adipose tissues and adipocytes. Comparison of white, beige and brown adipocytes regarding their morphology, primary function, uncoupling protein 1 (UCP1) expression (brown staining), mitochondrial content, and capability to store fat and produce heat. White adipose tissue comprises unilocular white adipocytes characterized by a single large lipid droplet and a low number of mitochondria. Brown adipose tissue consists of brown adipocytes with small multilocular lipid droplets and high mitochondrial density. White adipocytes can adopt brown-like characteristics under specific stimuli, like cold exposure, a process called white adipose tissue beiging.

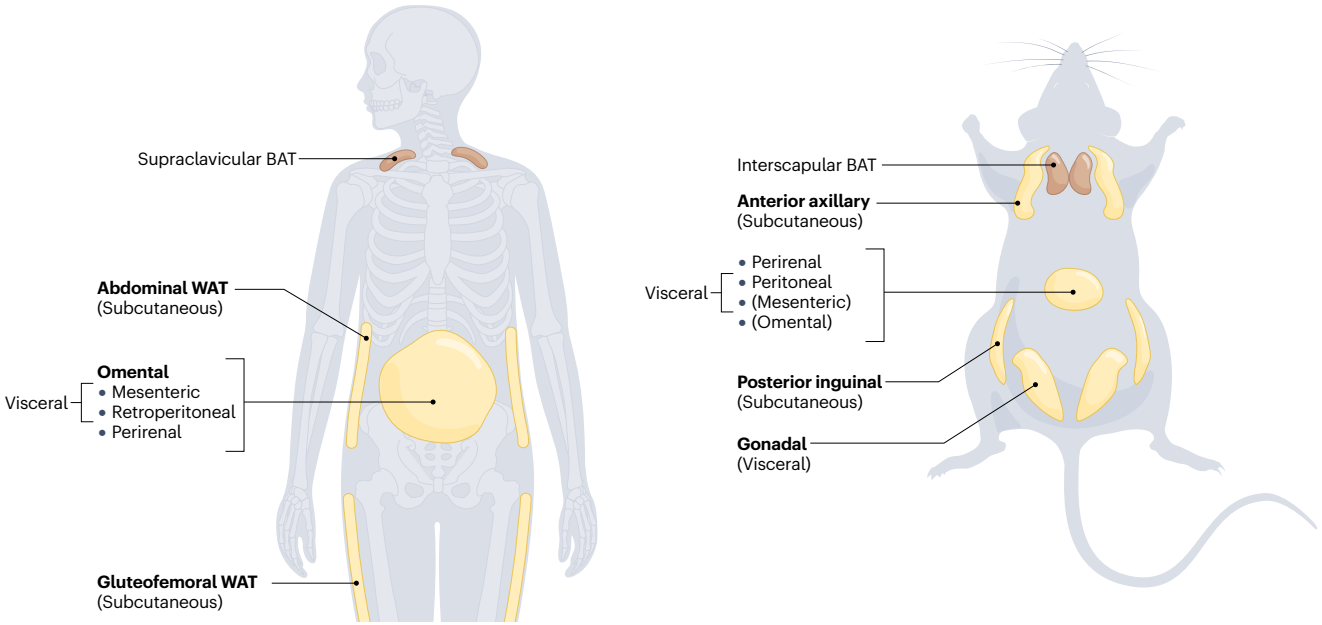


Fig. 3 | Different types of adipose tissues in humans and rodents. Adipose tissue in mice, like in humans, consists of multiple depots. Subcutaneous white adipose tissue (WAT) is spread under the skin throughout the body, whereas visceral WAT envelops the organs within the abdomen. However, whereas humans have two primary subcutaneous fat depots situated in the abdominal and gluteofemoral regions, the two main subcutaneous fat pads of mice are located anteriorly and posteriorly. In adult humans, most heat-producing beige adipose tissue (BAT) depots are found in the supraclavicular area of the neck. In contrast, the interscapular depot is the most dominant BAT in mice. Notably, BAT is more pronounced and visible in adult mice compared to adult humans. The gonadal WAT depots, found near the ovaries and testes, are often used as a representation of visceral WAT in research.

oxidation of fatty acids in skeletal muscle but did not affect glucose uptake[54]. These findings suggest that this batokine represents a novel class of circulating factors induced by exercise, which might contribute to the metabolic changes that occur during physical activity.

Sleep

Sleep is an often overlooked environmental factor that can affect energy metabolism. In humans, lack of sleep or poor sleep quality has been associated with an increased risk of obesity and metabolic disorders[56,57]. Sleep deprivation can disrupt the regulation of appetite hormones, leading to increased hunger and food intake[58–60]. In fact, blood samples from people who get little sleep show similar metabolic profiles to those of individuals with obesity[61]. In addition, sleep deprivation can impair glucose metabolism and insulin sensitivity, which can contribute to the development of type 2 diabetes. Interestingly, long sleep duration was also associated with an elevated risk of type 2 diabetes in humans[62,63].

One important connection affected by sleep deprivation is the hypothalamic–pituitary–adrenal axis, responsible for the release of the stress hormone cortisol, which regulates glucose metabolism and appetite[64]. Chronic sleep deprivation can lead to dysregulation of the hypothalamic–pituitary–adrenal axis, resulting in increased cortisol release and impaired glucose metabolism in humans[65]. Another important pathway is the circadian clock system, which regulates the timing of physiological processes, including metabolism. Sleep deprivation can disrupt the circadian clock system, leading to dysregulation of energy metabolism. In mice, this dysregulation is mediated by several genes, including *Clock*, *Bmal1*, *Dec*, *Per1* and *Cry1*, which are involved in the regulation of circadian rhythm[66,67].

Sleep deprivation can also impair insulin signalling and glucose metabolism through the AKT pathway. AKT is a key regulator of glucose metabolism, and sleep deprivation has been shown to decrease AKT phosphorylation and impair glucose uptake in adipocytes and muscle cells in both humans and mice[68,69].

Finally, sleep deprivation can affect the regulation of appetite hormones, including ghrelin and leptin, in humans[70–72]. Ghrelin is a hormone that stimulates appetite, and sleep deprivation has been shown to increase ghrelin levels, leading to increased hunger and food intake[70]. Leptin is a hormone that signals satiety, and sleep deprivation has been shown to decrease leptin levels, further contributing to increased appetite in humans[71,72].

Gut microbiota

The gut microbiota is a complex ecosystem of microorganisms encompassing bacteria, viruses, fungi, protozoa and archaea that reside in the gastrointestinal tract. Gut bacteria are by far the most extensively studied and understood members of this community owing to their culturability, relatively large genome size, intricate functional diversity and promising therapeutic potential. Although it is important to recognize that other microorganisms in the gut also exert a substantial influence on gut health and disease and are rightfully gaining increasing attention from researchers, this Review primarily concentrates on the bacterial community within the gut and, for convenience, can be referred to as 'gut microbiota', in alignment with current research trends.

The gut microbiota can have a substantial effect on energy metabolism by modulating the absorption and utilization of nutrients, regulating appetite, and influencing the development and function of adipose tissue[73]. In addition, the gut microbiota can produce a wide

range of metabolites that can influence energy metabolism, including short-chain fatty acids (SCFAs), bile acids and different bioactive lipids, including endocannabinoids (eCB), oxylipins and amino acid derivatives[3,4,38].

The gut microbiota has been implicated in the development of obesity and metabolic disease. For example, studies in germ-free mice have shown that the absence of gut microbes can protect against diet-induced obesity and improve glucose tolerance[74,75]. In addition, the gut microbiota has been shown to regulate the development and function of adipose tissue in mice[76–78]. For example, specific gut microbiota can promote or abolish the browning of WAT, leading to increased energy expenditure and improved metabolic health in mice[79–81]. In addition, targeting the gut microbiota using prebiotics, probiotics or postbiotics has emerged as a potential therapeutic strategy for the treatment of obesity and metabolic disease (Box 2). A prebiotic is a "substrate that is selectively utilized by host microorganisms conferring a health benefit"[82]. Probiotics are "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host"[83]. Postbiotics are the "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host"[84]; however, this definition has been challenged and debated in the literature over the past 2 years as some definitions also consider the metabolites produced by probiotics or other gut microbes[85,86].

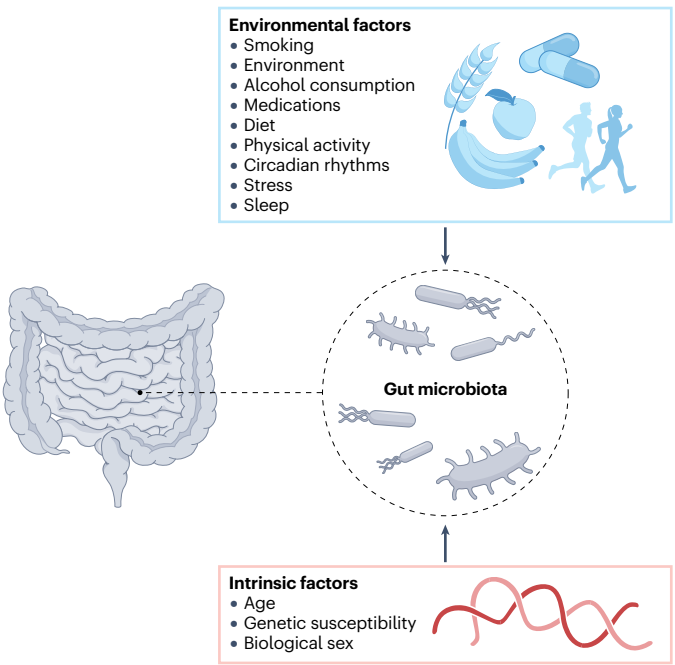


Fig. 4 | Environmental factors and intrinsic factors affecting the gut microbiota composition. The gut microbiota is a dynamic ecosystem, and its composition and function are influenced by multiple environmental and external factors such as diet, smoking, drug use, sleep, exercise and emotional stress. However, the extent of modulation caused by changes in these factors can vary greatly among individuals. This variability is influenced by the initial composition of the gut microbiota and intrinsic factors like age, biological sex and genetic susceptibility. This delicate balance results from a complex interplay between our lifestyle choices and inherent characteristics, and any disruption can profoundly affect our overall health.

Strikingly, the environmental factors mentioned earlier and affecting energy, such as diet, sleep and exercise, are all associated with changes in the gut microbiota composition in mice and humans[87–94] (Fig. 4). More importantly, several preclinical studies have shown that the gut microbiota might be one of the key factors contributing to their effect on energy metabolism by acting via changes in several metabolites such as bile acids, SCFAs, bioactive lipids and others, which will be described in the next section (Fig. 4).

Microbiota-related compounds influencing adipose tissue metabolism

Fasting-induced adipose factor

Fasting-induced adipose factor (FIAF), also known as angiopoietin-like protein 4 (ANGPTL4), is a circulating protein produced by various tissues, including the intestine, liver and adipose tissue, in response to fasting[95], and it is the main site of action for peroxisome proliferator-activated receptor (PPAR) proteins[96].

FIAF has been shown in mice to have a role in the regulation of lipid metabolism by inhibiting lipoprotein lipase (LPL), the rate-limiting enzyme for the hydrolysis of the triglyceride core in circulating lipoproteins, thereby decreasing the uptake of fatty acids into adipose tissue and muscle[97].

Mouse studies have suggested that the gut microbiota regulates FIAF production. FIAF is constitutively expressed in germ-free mice[74], and conventionalization (colonization with the gut microbiota of non-germ-free mice) decreased FIAF expression and increased LPL activity, resulting in increased body fat mass[76]. Moreover, germ-free mice with the *Fiaf* gene knocked out lost their resistance to obesity induced by a high-fat diet[74]. However, it is crucial to approach these findings with caution. Although initial studies on germ-free mice piqued substantial interest over the past two decades regarding the involvement of the gut microbiota in obesity development, its role remains ambiguous[74,76]. Current findings have challenged the widely held belief that the absence of gut microbiota inherently confers resistance to obesity, with divergent outcomes potentially linked to the source of dietary fat employed[98,99]. Markedly, replication attempts of a seminal study failed to mirror the original findings, leaving the influence of the absence of the gut microbiota on obesity still inconclusive[100]. This evidence underscores the complexity of the relationship between gut bacteria and metabolic diseases and suggests the need for further exploration. Whether FIAF production has a causal role in the gut microbiota-mediated effects on fat storage is still debated, especially as high-fat diet-induced obesity in germ-free mice only increased protein expression of FIAF in the intestine but not in the circulation[98].

Several studies have shown that the administration of certain bacteria can increase circulating FIAF levels in mice and increase its expression in human intestinal epithelial cells[101], suggesting that modulation of the gut microbiota can influence FIAF production.

The exact mechanism by which the gut microbiota regulates FIAF protein expression is still not fully understood, although FIAF also seems to have a crucial role in the central regulation of energy metabolism via inhibition of hypothalamic AMPK activity in mice[102]. Whether the gut microbiota regulates hypothalamic FIAF is unknown.

SCFAs and key receptors

Humans do not possess the digestive enzymes required to break down dietary fibres. Consequently, undigestible carbohydrates remain unaffected as they pass through the upper gastrointestinal tract and reach the large intestine, where they become available for fermentation by

Box 2

Microbiota-targeted approaches to change adipose tissue metabolism

All the dietary components listed here have been described to increase the beiging or browning of adipose tissue and affect the microbiota (for reviews, see refs. 254–256). They all protect against diet-induced obesity in mice. Most of these compounds act in both brown adipose tissue (BAT) and white adipose tissue by changing the same markers of adipose browning and fatty oxidation, such as increasing levels of uncoupling protein 1 (UCP1), DIO2, CPT1α, Cidea, peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α), SIRT1 and BMP7. Some of them increase cold-induced thermogenesis and mitochondrial amount and/or activity.

Most studied dietary components

- **Resveratrol:** also known as trans-3,5,4′-trihydroxystilbene, an organic compound categorized as a natural polyphenol. It is predominantly present in plants and plant-derived items such as *Polygonum cuspidatum*, various fruits, including grapes and berries, peanuts, and red wine[257–259].
- **Capsaicin:** an alkaloid compound found in pepper[260,261].
- **Quercetin:** a prominent flavonoid that can be commonly found in the human diet[262,263], present in apples, berries and onions.
- **Epigallocatechin-3-gallate:** a polyphenolic compound present in the unfermented dried leaves of the plant *Camellia sinensis*[264].
- **Berberine:** a naturally derived alkaloid present in specific flowering plants such as *Berberidaceae*, *Coptis* rhizomes and *Hydrastis canadensis*, utilized in traditional Chinese medicine[265–267].
- **Rhubarb extract:** an anthraquinone-rich crude extract derived from *Rheum palmatum* (rhubarb) roots[268,269].
- **Camu Camu (*Myrciaria dubia*):** an Amazonian fruit with a unique phytochemical profile[270].

Specific bacteria

- ***Akkermansia muciniphila*:** has been shown to increase browning, fatty acid oxidation, and BAT activity[136,271–273] and is linked with an increased gut barrier function.
- ***Dysosmobacter welbionis* J115^T:** is a butyrate producer recently identified and described to decrease BAT whitening and to increase mitochondrial activity likely by producing several bioactive lipids, including 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME)[204,205].

Several other strains have been proposed, although studied only once or not confirmed, and are therefore not shown in this box.

anaerobic bacteria[103,104]. This fermentation process leads to the production of various groups of metabolites, of which SCFAs are the primary group[105]. The amount and type of fibre consumed have substantial effects on the diversity and composition of the gut microbiota, which in turn affects the production of SCFAs[106].

SCFAs, of which acetate, butyrate and propionate are the dominant forms in the gut, are an important source of additional energy acquisition from undigested food. It has been estimated that SCFAs can provide up to 10% of the daily calories in humans, and colonocytes use SCFAs, especially butyrate, as their preferred energy source[107].

In addition, gut-derived SCFAs can be transported across colonocytes into the bloodstream, in which they are mixed with endogenous SCFAs (produced and released by tissues and organs) and from where they exert various effects on lipid, glucose and cholesterol metabolism in multiple tissues by acting as substrates or signalling molecules[3] (Fig. 5).

Adverse effects on health have been described in humans and mice for both low and excessive concentrations of SCFAs, although it remains unclear what the optimal levels of SCFAs would be in the body. To prevent excessive SCFA levels in the blood, the liver effectively absorbs most SCFAs from circulation[108]. In the liver, acetate is used as an energy source and serves as a substrate for the synthesis of long-chain fatty acids and cholesterol, and propionate acts as a precursor for gluconeogenesis[108].

Low SCFA concentrations have been associated in humans, mice and rats with the development of chronic metabolic disorders such as obesity, insulin resistance and diabetes[109–112], and studies in mice and rats have confirmed that dietary fibre or SCFA supplementation can alleviate the development of high-fat diet-induced obesity[3]. The underlying mechanisms are believed to engage several pathways.

One such mechanism is the role of SCFAs as signalling molecules. SCFAs, particularly butyrate and propionate, act as signalling molecules that can modulate the secretion of various hormones involved in appetite regulation, satiety and energy expenditure[108]. For instance, SCFAs can stimulate the release of glucagon-like peptide 1 (GLP1), peptide YY (PYY) and leptin[108,113]. GLP1 and PYY are hormones that promote satiety and reduce food intake, whereas leptin helps regulate energy balance by signalling the brain about energy stores. Furthermore, SCFAs can interact with G protein-coupled receptors (GPRs), particularly GPR41 and GPR43, on the surface of enteroendocrine L cells to stimulate the secretion of gut peptides[108,113] (Fig. 5). Besides the direct effect of SCFAs on the stimulation of the secretion of gut peptides involved in appetite regulation, it has also been proposed that SCFAs trigger intracellular signalling pathways upon activation of these receptors and eventually affect energy metabolism, inflammation and insulin sensitivity in different cell types (that is, white and brown adipocytes, hepatocytes, neurons, and immune cells)[109,110].

However, the relationship between SCFAs and adipose tissue is complex and not fully understood. For example, some studies have suggested that elevated SCFA concentrations might contribute to the development of obesity and insulin resistance, whereas others have found that SCFAs can improve insulin sensitivity and aid in weight loss

in vivo in mice, rats and humans[108,113–117]. Additionally, the effects of individual SCFAs on adipose tissue metabolism can vary. For instance, butyrate has been shown, both in vitro and in vivo, to induce adipogenesis through GPR43 activation, whereas propionate stimulates lipogenesis in mature adipocytes via GPR41 activation[118–122].

Indeed, in adipose tissue, activation of GPR41 and GPR43 can promote adipocyte differentiation and adipogenesis, leading to the formation of new adipocytes (hyperplasia) and increased adipose tissue mass[121]. The exact effect of SCFAs on BAT remains poorly explored. One study showed in vitro that acetate promotes the upregulation of both gene and protein expression of adipocyte protein 2 (AP2; a marker of adipocyte differentiation), PGC1α and UCP1 in mouse brown adipocytes, consequently increasing mitochondrial biogenesis, and these effects were impaired in cells with reduced GPR43 expression[123]. However, in human white adipocytes, the results are different. Preadipocytes isolated from human omental adipose tissue cultured for 13 days and exposed to different GPR43 agonists (that is, physiological or synthetic) to study the effect on adipocyte differentiation did not show any effects on *AP2* gene expression and, eventually, differentiation. In contrast, troglitazone (a PPARγ agonist) increased *AP2* gene expression in these cells with a tendency to decrease *GPR43* gene expression ($P = 0.06$)[120]. This observation suggests that, unlike in mice, there is no relationship between GPR43 and adipocyte differentiation in humans. Additionally, the same researchers found that *GPR43* gene expression did not increase in adipose tissue from individuals with obesity but was mostly associated with tumour necrosis factor (TNF)-related inflammatory processes[120].

If we focus on butyrate, there are still mechanisms by which butyrate confers metabolic benefits in mice and humans that are not fully understood. In 2018, Li et al. investigated the effect of butyrate on appetite and energy expenditure to determine the extent to which these two factors contribute to the beneficial metabolic effects of butyrate and found that one acute oral administration of butyrate via intra-gastric gavage (but not intravenous injection) reduced food

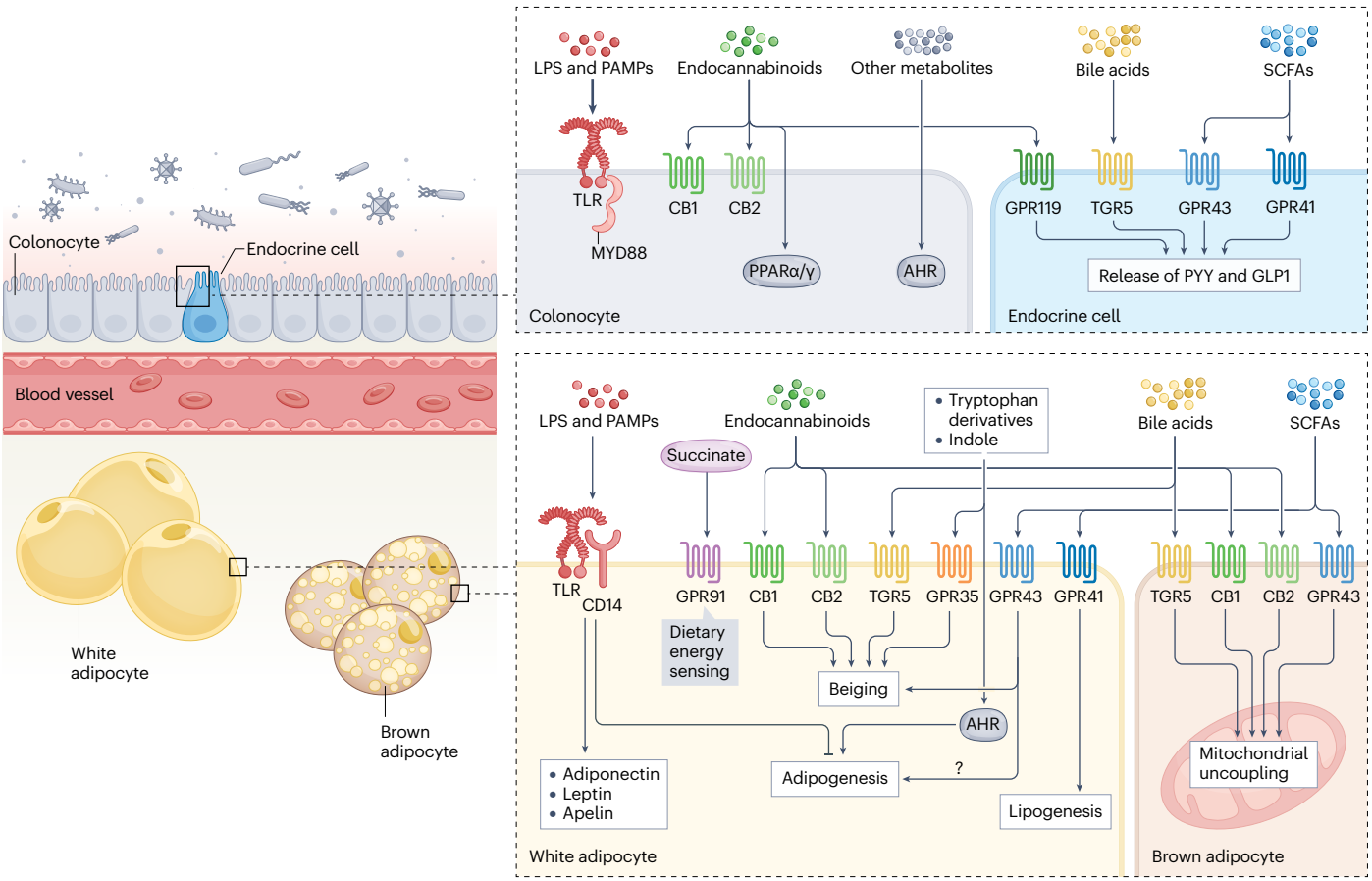


Fig. 5 | Molecular mechanisms and metabolites produced by the gut microbiota and acting on specific receptors in the intestine or the white and brown adipose tissues. Metabolites secreted by certain microbes (for example, lipopolysaccharides (LPS), pathogen-associated molecular patterns (PAMPs), endocannabinoids), generated by microbial digestion of dietary components (for example, short-chain fatty acids (SCFAs)) or by transformation of host-derived factors (for example, endocannabinoids and bile acids) can be sensed through various receptors and pathways to alter intestinal integrity and host health. Upper right panel refers to specific receptors expressed in colonocytes or enteroendocrine cells, the different specific receptors and their ligands coming from microbial metabolites or components. The lower right panel depicts the receptors expressed in white and brown adipocytes, the specific ligands coming from microbial metabolites or components, and the specific metabolic effects induced by the activation of these receptors. AHR, aryl hydrocarbon receptor; CB, cannabinoid receptor; CD14, cluster of differentiation 14; GLP1, glucagon-like peptide 1; GPR, G protein-coupled receptor; MYD88, myeloid differentiation primary response 88; PPAR, peroxisome proliferator-activated receptor; PYY, peptide YY; TGR5, Takeda G protein-coupled receptor 5; TLR, Toll-like receptor.

intake in overnight fasted mice within 1 h after refeeding[124]. Butyrate also suppressed the activity of orexigenic neurons in different areas of the brain. The researchers confirmed that chronic supplementation of butyrate in the drinking water prevented diet-induced obesity, hyperinsulinaemia, hypertriglyceridaemia and hepatic steatosis, but they primarily attributed this effect to a decrease in food intake. Butyrate also modestly enhanced fatty acid oxidation and activated BAT, leading to increased utilization of fatty acids, not solely owing to reduced food intake but mostly thanks to an augmented sympathetic outflow to BAT. The investigators finally found that the effects of butyrate on food intake and the stimulation of metabolic activity in BAT were abolished by subdiaphragmatic vagotomy[124]. In conclusion, these findings suggest that butyrate acts on the gut–brain neural circuitry to improve energy metabolism by reducing energy intake and enhancing fatty acid oxidation through the activation of BAT (Figs. 4 and 5).

Additionally, SCFAs can influence the epigenetic regulation of genes related to metabolism and adipose tissue development such as histone deacetylases and DNA methyltransferases[125]. These enzymes modify the chromatin structure and DNA methylation status of target genes, altering their accessibility and affecting their transcriptional activity[125]. By influencing gene expression patterns, SCFAs can promote metabolic homeostasis and mitigate the development of metabolic disorders (Fig. 5).

LPS and other pathogen-associated molecular patterns

Low-grade inflammation is one of the hallmarks of obesity and related metabolic disorders[126]. The origin of this inflammation was initially linked with the gut microbiota due to the development of metabolic endotoxaemia[127]. Metabolic endotoxaemia is also known as endotoxin-induced metabolic inflammation and refers to a condition characterized by increased levels of circulating lipopolysaccharides (LPS; frequently referred to as endotoxins) in the bloodstream, which can lead to low-grade chronic inflammation and metabolic dysfunction[128]. LPS are molecules found on the outer membrane of certain types of bacteria such as Gram-negative bacteria. Under normal circumstances, the gut barrier prevents the translocation of endotoxins from the gut lumen into the bloodstream[128,129] (Fig. 5). However, besides typical infections or inflammatory bowel diseases, certain factors can compromise the integrity of the gut barrier, enabling endotoxins to leak into the circulation. These factors include a high-fat diet[78], excessive alcohol consumption[130], obesity[131–133], hyperglycaemia[134] and lack of dietary fibres[135], all contributing to distinct modifications in the integrity of the gut barrier. These alterations involve changes in the arrangement and positioning of tight junction proteins, variations in the production of antimicrobial peptides, and modifications in the composition of the mucus layer[136–139].

Several mechanisms have been proposed by which gut-derived compounds, such as LPS, can influence adipose tissue metabolism in mice, rats and humans. One of these is the stimulation of inflammatory pathways via Toll-like receptor 4 (TLR4) and its co-receptor CD14 triggering immune responses in adipose tissue[77,127,140,141]. When exposed to LPS, adipocytes and preadipocytes can undergo changes that interfere with normal adipogenesis. For instance, LPS can inhibit the differentiation of mouse preadipocytes into mature adipocytes by disrupting the expression of key transcription factors involved in adipogenesis such as PPARγ and CCAAT–enhancer-binding protein-α (CEBPA)[77,142–144]. LPS triggers the release of pro-inflammatory cytokines, such as TNF, which interferes with the differentiation process through the WNT–β-catenin–T cell factor 4 (TCF4) pathway. Specifically, in vitro, TNF enhances TCF4-dependent transcriptional activity and promotes the stabilization of β-catenin and of a pro-inflammatory environment that hinders adipogenesis[145,146] (Fig. 4). Besides the direct effect of LPS and inflammation on the processes of adipogenesis, it has also been shown in mice that LPS can change the secretion of different adipokines, including increasing the secretion of apelin, adiponectin and leptin, which have crucial roles in regulating energy metabolism and inflammation but also adipogenesis[147,148]. In vitro, LPS might also have a role in impaired adipogenesis and the onset of cellular senescence in adipose tissue, particularly in the context of obesity and ageing[149].

However, it is important to note that the effects of LPS on adipogenesis can vary depending on the concentration and duration of exposure and the specific cellular context. Indeed, some in vivo and in vitro studies have shown that LPS can increase preadipocyte proliferation and adipogenesis via JAK–STAT and AMPK-dependent cPLA2 protein expression but also through a CD14-dependent mechanism[150,151]. Furthermore, although LPS-induced inflammation can interfere with adipogenesis, the relationship between LPS, adipose tissue and metabolic disorders is complex and still an active area of research. Although there is evidence showing that germ-free mice are protected against diet-induced obesity and exhibit reduced WAT inflammation and insulin resistance[74,75,152], it is not clear which microbial factors promote WAT inflammation. To investigate whether LPS in the gut is sufficient to promote glucose and insulin tolerance and macrophage accumulation in WAT, Caesar et al. mono-colonized germ-free mice with *Escherichia coli* and found that the colonization of the gut with this LPS-producing bacteria led to impaired glucose metabolism, increased macrophage accumulation, and polarization towards the pro-inflammatory M1 phenotype in WAT[140]. Conversely, mono-colonization of germ-free mice with an *E. coli* expressing LPS but with reduced immunogenicity (that is, *E. coli* MLK1067) did not induce macrophage accumulation or inflammation in the WAT[140].

Similarly, data suggests that LPS from specific bacteria can have an antagonistic effect on TLR4 but still contribute to endotoxaemia as measured by endotoxin units. Anhê et al. found that LPS from *E. coli* impaired the integrity of the gut barrier and exacerbated glycaemic control in mice[153]. However, when comparing equal endotoxin unit doses of LPS from other bacteria (for example, *Rhodobacter sphaeroides*), the researchers discovered that the mice did not have the same negative effects or even counteracted the dysglycaemia caused by an equivalent dose of LPS from *E. coli* LPS in obese mice[153]. These findings suggest that metabolic endotoxaemia should extend beyond the mere LPS load and consider specific characteristics of LPS molecules such as lipid A acylation.

Besides LPS, the disruption of the gut barrier associated with overweight and obesity is also linked with the translocation of other pathogen-associated molecular patterns and fat mass development. For example, studies have shown that peptidoglycans and lipopeptides can also contribute to the onset of metabolic disorders and individuals affected by obesity have been shown to have increased blood concentrations of peptidoglycans and lipopeptides[154]. Peptidoglycans are components of the bacterial cell wall found in both Gram-positive and Gram-negative bacteria. It has been demonstrated that bacterial peptidoglycan can induce lipolysis in adipocytes via activation of nucleotide-binding oligomerization domain-containing protein 1 (NOD1). This NOD1-mediated lipolysis involves the stress kinases (ERK1 and ERK2), PKA and NF-κB pathways, converging on hormone-sensitive lipase[155]. Endoplasmic reticulum stress inositol-requiring protein 1 has

been proposed as a key regulator of lipolysis and blood triglycerides during inflammation[156].

These data suggest that receptors of pathogen-associated molecular patterns, such as TLRs and NOD-like receptors, are a convergence point that can link immune responses associated with obesity to hyperlipidaemia and insulin resistance, at least in mice[157].

Flagellin (a protein component of bacterial flagella), bacterial DNA and bacterial lipoproteins are molecules also acting on specific TLRs and are released into the bloodstream owing to increased gut permeability or translocation from the gut in obesity and diabetes[158–160]. However, the role of these compounds in the onset of metabolic disorders remained controversial. For instance, mice with a genetic deficiency in *Tlr5* (the receptor for bacterial flagellin) have a modified microbiota species composition and display characteristics associated with metabolic syndrome[161]. Also linked to specific alterations in the composition of the gut microbiota, mice lacking *Tlr2* (a pattern-recognition receptor that detects many ligands from bacteria) exhibited a metabolic syndrome phenotype characterized by insulin resistance, glucose intolerance, fat mass and weight gain as well as elevated levels of circulating LPS and subclinical inflammation[162]. Finally, mice lacking *Nod2* (detecting peptidoglycan) showed higher inflammation in adipose tissue and liver, exacerbated insulin resistance during high-fat diet feeding, and augmented translocation of commensal bacteria from the gut into adipose tissue and liver[163].

Altogether, these findings underscore the importance of investigating the detection of bacterial components and better understanding the connections between gut microbes, inflammation and adipose tissue in the context of obesity and type 2 diabetes.

Tryptophan derivatives

Tryptophan can be metabolized into different metabolites in the gut microbiota and tissue cells. Bacterially derived tryptophan-metabolite indoles, such as indole-3-propionate (IPA), are present at lower levels in blood samples from individuals with obesity than in samples from controls with normal weight. The kynurenine pathway is responsible for the degradation of tryptophan into kynurenine (Kyn), kynurenic acid (Kyna) and quinolinic acid. Conversely, compelling evidence indicates that increased levels of Kyn are observed in the plasma of individuals with obesity, which might be attributed to the heightened enzymatic activity of indoleamine 2,3-dioxygenase 1 (IDO1)[164,165]. However, several intestinal bacteria encode enzymes homologous to those of the eukaryotic Kyn pathway[166]. Tryptophan derivatives and indole from the gut microbiota can regulate adipose tissue development by promoting the differentiation of preadipocytes into mature adipocytes by activating the aryl hydrocarbon receptor (AHR) signalling pathway (Fig. 4). The AHR signalling pathway is involved in the regulation of adipogenesis and adipocyte metabolism[167,168]. However, the main source of Kyn and its effect on metabolic syndrome have not been fully investigated. Along these lines, Agudelo et al. demonstrated that Kyna, through the activation of GPR35, promoted fatty acid oxidation, thermogenesis and anti-inflammatory gene expression in adipose tissue, leading to a suppression of weight gain in high-fat diet-fed mice and an improvement in glucose tolerance[169] (Fig. 5). Moreover, Kyna and GPR35 enhanced the expression of PGC1α and cellular respiration and increased gene expression levels of *Rgs14* in adipocytes, resulting in enhanced signalling of β-adrenergic receptors. Conversely, the genetic deletion of *Gpr35* caused progressive weight gain, glucose intolerance and heightened susceptibility to a high-fat diet. Additionally, *Gpr35* knockout mice exhibited compromised adipose tissue browning induced by exercise. These findings unveiled a novel pathway through which gut microbiota-derived metabolites communicate to regulate energy homeostasis[169]. As stated earlier, increased enzymatic activity of IDO1 has been observed in obesity, but its role in metabolic disease remains poorly explored. A study in mice and humans revealed that obesity is linked to heightened enzymatic activity of IDO1 in the intestine, leading to a shift in tryptophan metabolism from indole derivative and IL-22 production to kynurenine production[170]. It was shown that deleting or inhibiting IDO1 improved insulin sensitivity, preserved the gut mucosal barrier, reduced metabolic endotoxaemia and inflammation, and changed lipid metabolism in the liver and adipose tissues[170].

Besides the gut microbiota, data suggest that adipose tissue might be a major direct source of Kyn. It has been shown in vivo that the IDO1 gene and protein are expressed in adipocytes. Depleting *Ido1* in adipocytes prevented the accumulation of Kyn and protected mice from obesity. Interestingly, the mechanism behind this effect still involves the activation of AHR, as genetically removing *Ahr* from adipocytes negates the impact of Kyn[171] (Fig. 5).

It was also demonstrated that tryptophan-derived metabolites produced by the gut microbiota controlled the expression of the miR-181 family in white adipocytes in mice to regulate energy expenditure and insulin sensitivity[172]. Moreover, dysregulation of the gut microbiota–miR-181 axis contributes to the development of obesity, insulin resistance and WAT inflammation in mice. It was found in a cohort of children, categorized by their weight percentiles ($n = 19$ with a healthy weight, $n = 19$ with obesity), that miR-181 expression in WAT and the plasma abundance of tryptophan-derived metabolites were dysregulated in obesity[172].

Bioactive lipids

Bioactive lipids are a class of signalling molecules derived from lipids (fatty acids, phospholipids and sphingolipids) with crucial roles in various physiological and pathological processes within the human body[173]. They are also involved in a wide range of biological activities, including inflammation, pain modulation, blood pressure regulation, cell growth and differentiation, apoptosis (programmed cell death), and immune responses[174,175]. Bioactive lipids produced by both the host and gut microbiota can influence the composition and activity of the microbiota and various host metabolic processes[176,177].

Bile acids. Bile acids are produced by the liver but are highly regulated by the activity and composition of the microbiota[178,179]. Primary bile acids, such as cholic acid and chenodeoxycholic acid (CDCA) in humans (and muricholic acid in mice and rats), can be conjugated with glycine or taurine before being released into bile and stored in the gallbladder[178–180]. When we consume food, bile acids are released into the small intestine to aid in the digestion and absorption of dietary fat. Approximately 95% of the bile acids in the intestine are reabsorbed in the ileum and returned to the liver for re-secretion. Only a small portion of bile acids escapes this efficient cycle and reaches the colon. From there, they are either passively reabsorbed into circulation or excreted through faeces[181]. Although the primary function of bile acids is to regulate the digestion and absorption of cholesterol, triglycerides and fat-soluble vitamins, it has been discovered in both mice and humans that they also serve as signalling molecules, functioning as hormones[179]. The effect of bile acids on the regulation of glucose, lipid and energy metabolism has been previously reviewed[179,182] and will be briefly discussed here (Fig. 5).

Among the different receptors, G protein-coupled bile acid receptor 1 (also known as Takeda G protein-coupled receptor 5 (TGR5)) is found in various tissues and is highly expressed in BAT. TGR5 has a role in transmitting signals and activating gene expression related to the metabolism of lipids and carbohydrates as well as to energy expenditure and inflammation[183]. In adipocytes isolated and differentiated from *Tgr5*$^{+/+}$ mice, the bile acid mimetic INT-777 showed a dependent activation of *Tgr5*, increased mitochondrial biogenesis, and improved mitochondrial function and mitochondrial β-oxidation by both increasing lipolysis and substrate availability[184]. A pilot study performed on 12 healthy women investigated the effect of orally supplementing CDCA on BAT activity. The researchers found that administration of CDCA for 2 days resulted in higher BAT activity and whole-body energy expenditure. Using primary human brown adipocytes, the researchers also found that CDCA or specific TGR5 agonists increased mitochondrial uncoupling. Strikingly, these effects were not observed in primary human white adipocytes[185].

It is worth noting that signalling through the TGR5 receptors expressed on the enteroendocrine L cells has also been associated in both mice and humans with the release of gastrointestinal hormones like PYY and GLP1, which are important for maintaining energy and metabolic balance but mostly by acting on food intake[186–188] (Fig. 5).

Endocannabinoids. The eCB system is known for its wide range of physiological effects, including the regulation of appetite (that is, energy metabolism), glucose and lipid metabolism, as well as its role in immunity, inflammation, and interactions between microbiota and the host[77,176]. The identification of the first endogenous cannabinoid receptor type 1 (CB1) occurred in 1988 when it was found to be activated by the psychoactive compound Δ9-tetrahydrocannabinol from *Cannabis sativa*[189]. Subsequently, the discovery of a second receptor, CB2, occurred in 1993 (ref. 190). Both receptors belong to the GPR family and share similar signalling mechanisms. The first endogenous endocannabinoid discovered was anandamide (*N*-arachidonoylethanolamide), which is both a CB1 and CB2 ligand and would later become known as part of a larger group of bioactive lipids known as *N*-acylethanolamines. 2-Arachidonoylglycerol was the second endogenous cannabinoid receptor ligand identified[176]. Since the initial discovery of these two major compounds, the eCB family has expanded beyond those with specific activity on CB1 and CB2 receptors. Several pioneering studies in mice, rats and humans have indicated the involvement of eCBs in the metabolism of adipose tissue and that activation of the eCB system promotes adipogenesis[191–194] (Fig. 5).

However, in 2010, researchers made a substantial discovery regarding the regulation of gut barrier function, gut microbiota and adipose tissue metabolism, showing that the eCB system had a major role. Specifically, in mice, there was an increased presence of anandamide during obesity and diabetes, which triggered gut permeability through CB1-dependent mechanisms[77,195]. Furthermore, when the eCB system was pharmacologically activated using a potent eCB agonist, it increased adipogenesis and disruption of the gut barrier[196]. This increase in permeability further amplified the levels of LPS (that is, metabolic endotoxaemia) in the bloodstream, disturbing the gut barrier and affecting both the eCB system in the entire intestine and adipose tissues[77] (Fig. 4). In the pathological state of obesity, the altered eCB tone and elevated LPS levels contributed to the dysregulation of adipogenesis, perpetuating the initial imbalance and establishing a harmful cycle contributing to the onset of an altered adipose tissue metabolism. This was a novel pathophysiological mechanism connecting the gut microbiota to the eCB system in the intestine and having a substantial role in regulating adipogenesis. Moreover, this finding demonstrates that adipogenesis is influenced by a feedback loop involving LPS and the eCB system. Given that obesity is commonly associated with changes in eCB system tone (that is, alterations in the levels of eCBs, the expression of CB1 and CB2 receptors, and the levels of enzymes involved in both synthesis and degradation of eCBs), elevated plasma LPS levels, disrupted composition of the gut microbiota and impaired adipose tissue metabolism, it is plausible that the altered eCB system tone observed in obesity is a consequence of a malfunction or an ongoing vicious cycle within the pathways governing the eCB system.

After this discovery, numerous independent mouse studies provided further evidence for the connection between the gut microbiota, adipose tissue metabolism and the eCB system. Genetically obese and diabetic mice (*ob/ob* and *db/db*, respectively) displayed a substantial shift in their gut microbiota composition linked to changes in overall tissue metabolism and eCB system function[147,197]. This observation was also shown in diet-induced obesity mouse models and germ-free mice[92,198,199]. Collectively, these findings strongly support the existence of a relationship between specific bioactive lipids from the eCB system, the gut microbiota, adipose tissue development and intestinal function.

Finally, to delve deeper into the underlying mechanisms and investigate whether the synthesis of some of these bioactive lipids could contribute to the onset of metabolic disorders and alterations in the gut microbiota, researchers generated various mouse models selectively deactivated for N-acylphosphatidylethanolamine-hydrolysing phospholipase D (NAPEPLD), a key enzyme involved in the synthesis of these lipids in adipocytes[80]. Mice that lacked *Napepld*, specifically in their adipocytes, exhibited spontaneous development of obesity, insulin resistance and inflammation despite being on a normal calorie diet. These mice were also more susceptible to metabolic disorders induced by a high-fat diet. Deletion of *Napepld* specifically in adipocytes reduced the thermogenic programme in adipose tissue, known as browning or beiging, and caused a marked alteration in the gut microbiota composition[80]. When the microbiota from these *Napepld*-deleted mice was transferred to germ-free recipient mice, it replicated the overall phenotype, including a lower browning or beiging, indicating a causal role of the gut microbiota[80]. Collectively, these findings suggest that the eCB system, specifically the NAPEPLD enzyme, interacts with the gut microbiota through the production of bioactive lipids, and any dysregulation of this enzyme can lead to metabolic complications.

In conclusion, all the evidence indicates a bidirectional communication between the host eCB system and the gut microbiota. However, further investigations are necessary to unravel the remaining mysteries of this relationship. Adding to the complexity, bioinformatics analysis of human microbiome data has shown that the gut microbiota itself can produce specific N-acyl amides that are structurally similar to human GPCR ligands[200]. Gnotobiotic mice colonized with bacteria expressing the synthase for N-acyl serinols showed decreased blood glucose levels in an oral glucose tolerance test, consistent with action on host GPR119 (ref. 200). This discovery opens exciting opportunities for exploration of the interaction between the microbiota and the host, presenting several potential new targets for therapy.

Oxylipins. Oxylipins are a diverse group of bioactive lipid molecules derived from the oxidation of polyunsaturated fatty acids. These compounds act as signalling molecules and have crucial roles in various physiological processes, including inflammatory processes such as

those that occur in obesity[201]. Studies in rats have demonstrated the effect of the gut microbiota in regulating these metabolites, thereby suggesting an effect of the gut microbiota on oxylipin-mediated inflammatory processes[202].

12,13-DiHOME (also known as isoleukotoxin diol) is an oxylipin formed from linoleic acid by the action of cytochrome P450 and soluble epoxide hydrolase enzymes. 12,13-DiHOME is produced mainly by BAT or beige adipose tissue, and factors like exercise, diet and temperature influence its concentration in the body[54]. It has a role in regulating fatty acid uptake in adipose tissue and thermoregulation during cold exposure.

12,13-DiHOME concentrations were found to be lower in 28 adolescent men with obesity than in 28 men of the same age with normal weight, and increased with acute exercise[203]. In mice with obesity induced by a high-fat diet, administration of 12,13-diHOME for 2 weeks promoted fatty acid transport into BAT, decreasing circulating triglyceride concentrations and increasing gene expression of LPL (an enzyme that hydrolyses triglycerides found in lipoproteins) in BAT[55].

Interestingly, some gut bacteria can produce and secrete 12,13-diHOME. For example, 12,13-diHOME was identified among the several bioactive lipids produced by *Dysosmobacter welbionis*, and the administration of this bacterium to mice significantly ($P < 0.001$) reduced the whitening of BAT induced by a high-fat diet and increased mitochondrial activity[204,205].

Role of succinate and GPR91. Succinate is an intermediate in the tricarboxylic acid cycle, also known as the citric acid cycle or Krebs cycle, which is central to cell metabolism and energy homeostasis[206].

Succinate can escape this cycle and act as an extracellular ligand by binding to a GPR called succinate receptor 1 (SUCNR1), also known as GPR91, which is expressed in the kidney, liver, heart, retinal cells and many other tissues, leading to a wide array of physiological and pathological effects[207]. Through GPR91 on adipocytes, succinate is also involved in the regulation of metabolism[206]. Notably, succinate can be derived from microbial carbohydrate fermentation and serves as a catabolic metabolite[206]. The primary fermenters predominantly utilize the succinate pathway to produce propionate, making it the most prevalent biochemical pathway for propionate production. Additionally, succinate and propionate can arise as metabolites through the fermentation of amino acids[208] (Fig. 5). Furthermore, the importance of succinate as a vital microbial product in the advantageous metabolic effects of consuming dietary fibre has been uncovered in mice: this consumption leads to an augmentation of *Prevotella*-produced succinate[209,210]. Interestingly, it is known that inverse correlations exist between the abundance of *Akkermansia muciniphila*, which produces succinate as one of the primary metabolites during mucin degradation[211], and obesity, diabetes and related metabolic disorders[212]. Moreover, the introduction of other succinate producers, like *Parabacteroides distasonis*, has also proven effective in ameliorating metabolic dysfunctions associated with obesity in mice[213].

Using mouse and rat models of type 2 diabetes, obesity and hypertension, elevated concentrations of circulating succinate were also observed compared to healthy animals with normal weight[214]. Interestingly, contrary to rodents, hypertension and type 2 diabetes were not associated with elevated circulating succinate levels in human blood samples[214].

It was shown that GPR91 is highly expressed in WAT in mice and regulates adipose mass and glucose homeostasis[215]. By generating a *Gpr91*$^{-/-}$ mouse model, the loss of succinate receptor affected metabolism and body weight. However, the precise effects (increase or decrease in weight or cumulative fat content) varied depending on the specific experimental conditions. On a regular diet, *Sucnr1*$^{-/-}$ mice exhibited a smaller WAT compartment, smaller adipocytes, increased energy expenditure and improved glucose regulation. Surprisingly, the deletion of *Gpr91* did not alter adipogenesis but resulted in reduced lipid accumulation and smaller adipocyte size. Further evaluation of the metabolic changes due to *Gpr91* deletion using VO_2 tests revealed a reduced oxygen consumption rate in *Sucnr1*$^{-/-}$ mice compared to wild-type counterparts[215]. When *Sucnr1*$^{-/-}$ mice were fed a high-fat diet, they were protected from obesity only in the first couple of weeks. At later stages (after 16 weeks), the mice exhibited increased fat deposition, hyperglycaemia, reduced insulin secretion and enhanced hepatocyte damage compared to wild-type littermates. These findings suggest that GPR91 acts as a sensor for dietary energy and could be a potential therapeutic target for obesity, hypertension and diabetes[214].

Although not directly linked to overweight or obesity, data suggest an intricate relationship between Crohn's disease, gut bacteria and adipose tissue. A study found the presence of beige adipose tissue depots in Crohn's disease[216]. The study revealed that plasma succinate levels were significantly ($P < 0.0001$) higher in 17 individuals with active Crohn's disease than in 10 healthy controls. The expression of *SUCNR1* was higher in VAT, adipose-derived stem cells and adipose tissue macrophages from the active Crohn's disease group compared to the healthy controls or patients with inactive Crohn's disease ($n = 12$). Interestingly, treating adipose-derived stem cells with succinate increased the expression of several beige adipose tissue markers, including UCP1, in controls and patients with inactive Crohn's disease[216].

In conclusion, these findings indicate that succinate and bacteria have a role in triggering the transition from white to beige adipocytes in Crohn's disease; however, this remains to be explored in the context of obesity.

Adipose tissue microbiota

Current human studies have suggested that there is a microbiota signature in the adipose tissue of individuals and that this signature might be distinct according to the metabolic burden of the host[217–219]. In this section, we discuss this novel subject, focusing on the following aspects: (1) the methods and challenges of detecting and characterizing the adipose tissue microbiota; (2) the potential sources and mechanisms of microbial translocation from the gut to adipose tissue; (3) the diversity and functional roles of the adipose tissue microbiota in different fat depots and metabolic conditions; and (4) the implications and perspectives for future research and therapeutic interventions.

One of the main challenges of studying the adipose tissue microbiota is to ensure the reliability and validity of microbial detection methods. Several studies have used 16S ribosomal RNA (rRNA) gene-based bacterial quantification to identify and compare the microbial profiles in different adipose tissue depots and metabolic conditions. However, this approach has some limitations, such as the risk of contamination from environmental or reagent sources, the low sensitivity and specificity of some primers and probes, and the difficulty distinguishing between viable and dead bacteria[220]. Moreover, 16S rRNA gene-based methods cannot provide information on the functional capacity or activity of the adipose tissue microbiota, which might be more relevant for understanding its metabolic effect[221]. Although efforts have been made to overcome some of these obstacles by carefully controlling for contamination[218], complementary methods, such as metagenomics, metatranscriptomics, metabolomics and culture-based techniques,

will be needed to complement current studies and obtain a more comprehensive picture of the adipose tissue microbiota.

The origin and routes of microbial translocation from the gut to adipose tissue are not fully understood but several mechanisms have been proposed. One possibility is that bacteria or their components cross the intestinal barrier through increased intestinal permeability, often observed in obesity and type 2 diabetes[217]. Another possibility is that bacteria or their genetic material are actively transported by immune cells, such as macrophages or dendritic cells, that migrate from gut-associated lymphoid tissue to adipose tissue[217,222]. A third possibility is that bacteria or their components are carried by the portal vein or the lymphatic system to the liver or other organs, where they can affect local or systemic inflammation and metabolism[217,222].

The diversity and functional roles of the adipose tissue microbiota might vary depending on several factors, such as the anatomical location of the fat depot, the metabolic state of the host and the interaction with other host factors. For instance, Anhê et al. found that different adipose tissue depots (subcutaneous, mesenteric, omental and liver) had distinct microbial signatures in individuals with obesity with or without type 2 diabetes and that these signatures were independent of BMI (samples from 20 individuals with morbid obesity who had type 2 diabetes (average BMI of 50.2 ± 7.9 kg/m^2) were compared to samples from 20 individuals who had normoglycaemia (average BMI of 50.9 ± 9.1 kg/m^2))[218]. That same year, Massier et al. found evidence for tissue-specific quantitative, taxonomic and compositional bacterial signatures associated with inflammatory markers and metabolic traits in a tissue-dependent manner[217]. Similarly, Sun et al.[222] reported that individuals with obesity had higher bacterial load and lower bacterial diversity in SAT than individuals with normal weight and that these differences were associated with altered expression of genes involved in lipid metabolism and inflammation[217].

Another important challenge in the context of adipose tissue microbiota concerns the link between the presence of specific bacteria in breast milk, their origin and, eventually, the possible link with the development of 'pink' adipocytes, a distinct kind of adipocyte that can be found in the subcutaneous fat depots of mice during pregnancy and lactation[223]. These pink adipocytes, specialized cells that originate from subcutaneous white adipocytes, produce and release milk[223]. The growing body of evidence indicates that they undergo a process called transdifferentiation to become mammary gland alveolar epithelial cells[223]. Evidence also supports the hypothesis that transdifferentiation can occur from white to pink, pink to brown, and brown to myoepithelial cells in a reversible manner[223]. Strikingly, a microbiota with a distinct composition is found in human milk. Milk from healthy women typically has a low bacterial presence, primarily comprising *Staphylococcus*, *Streptococcus*, lactic acid bacteria and other gram-positive bacteria like *Corynebacterium*, *Propionibacterium* and *Bifidobacterium*, though DNA from strictly anaerobic bacteria can also be found[224–226]. It is structured by coordinated groups of microorganisms and interconnected networks[227,228]. One of the key unknowns is whether the alteration of the microbiota present in breast tissue and eventually in human milk can potentially affect mammary health, the breast adipose tissue and transdifferentiation from white to pink adipocytes. Notably, in addition to colostrum and milk, breast tissue of both women who lactate or not, might harbour a microbiota, which might have implications for breast cancer development, progression and treatment[227].

The study of the adipose tissue microbiota is a novel and promising field of research that might provide new insights into the pathophysiology and treatment of metabolic diseases[229]. However, many unanswered questions and challenges still need to be addressed. For example, what are the causal relationships between the adipose tissue microbiota and metabolic outcomes? How do diet, lifestyle, genetics, medications or other environmental factors influence the adipose tissue microbiota? How can we manipulate or modulate the adipose tissue microbiota to improve metabolic health? More longitudinal, interventional and mechanistic studies are needed to answer these questions as are standardized protocols for sampling, processing, analysing and reporting data on the adipose tissue microbiota.

Gut–adipose axis and the search for biomarkers in obesity and insulin resistance

Research into the complex interactions between gut microbiota and adipose tissue has unveiled a fascinating interplay that goes well beyond digestion and metabolism. As described earlier, the gut microbiota, a diverse community of microorganisms residing in the gastrointestinal tract, has been found to influence various physiological processes, including energy homeostasis, inflammation and insulin sensitivity.

The gut–adipose axis represents a bidirectional communication system that involves signalling molecules, metabolites and immune mediators exchanged between the gut microbiota and adipose tissue. Adipose tissue — once considered an inert energy storage depot — is now recognized as an active endocrine organ that releases adipokines, cytokines and other factors with systemic effects. On the other hand, the gut microbiota produces an array of metabolites influencing host metabolism and immune responses. This dynamic interplay between gut microbiota and adipose tissue opens new avenues for the identification of biomarkers related to obesity and insulin resistance. Potential biomarkers are summarized in Box 3.

The intricate crosstalk between gut microbiota and adipose tissue provides a fascinating insight into the complex mechanisms underlying obesity and insulin resistance. The potential biomarkers arising from this interplay hold promise for the identification of individuals at risk of metabolic disorders, enabling early interventions and personalized strategies to mitigate the effect of obesity and improve insulin sensitivity. Further research is warranted to unravel the precise molecular mechanisms underlying these interactions and to validate the utility of these biomarkers in clinical settings.

Moving from bench to bedside: key challenges

Although valuable insights into the crosstalk between the gut microbiota and adipose tissue have been gained over the past few years, translating findings from in vitro and animal studies to humans remains particularly challenging.

One major hurdle is the limitations that are inherent to animal models. Germ-free mice, which are raised without gut microbiota, provide insights into the role of certain gut bacteria or bacterial combinations. However, these mice lack microbial interactions during development and consequently have altered metabolism and compromised immune system function, which might not accurately reflect human physiology. Genetically obese mice (like *ob/ob* and *db/db* mice) have helped our understanding of the pathophysiology of obesity, but their genetic basis limits their translation to human obesity as leptin and leptin-receptor deficiencies are rare in humans and the mutations cause major disruptions of metabolic regulatory pathways[230]. High-fat diet obese mice, on the other hand, mimic some aspects of human obesity but fail to replicate the multifactorial nature of the disease[231]. Genetic and lifestyle factors have a substantial role in human obesity and are difficult to replicate in a laboratory.

Box 3

Biomarkers related to obesity and insulin resistance

- **Microbial diversity and composition.** Altered gut microbiota diversity and abundance of specific microbial taxa have been associated with obesity and insulin resistance. For instance, adipocyte diameter, glucose and surrogates of insulin sensitivity seemed tightly linked with the abundance of *Akkermansia muciniphila* in humans. Subcutaneous white adipocyte diameter was inversely associated with *A. muciniphila* abundance, and individuals with a high *A. muciniphila* abundance had a lower mean adipocyte size[274]. Although still under heavy debate because of the many confounding factors and the great inter-individual variations, the identification of certain microbial (core) signatures could serve as early indicators of metabolic dysfunction.
- **Metabolites.** Microbial metabolites, such as short-chain fatty acids, secondary bile acids and trimethylamine-N-oxide, can reflect gut microbiota activity and potentially predict obesity and risk of insulin resistance (for a review, see ref. 275). Increased levels of short-chain fatty acids have also been associated with decreased body weight, fat mass, waist circumference, fasting glucose, insulin resistance and inflammation[109]. Increased levels of secondary bile acids have been linked to decreased BMI, waist-to-hip ratio, fasting glucose, insulin resistance and inflammation. Increased levels of trimethylamine-N-oxide have been correlated with increased BMI, waist circumference, body fat percentage, fasting glucose, insulin resistance, blood pressure, inflammation and oxidative stress[3].
- **Adipokines and inflammatory markers.** Numerous circulating levels of adipokines and inflammatory markers, influenced by adipose tissue health, could serve as indicators of obesity-associated insulin resistance. Given the extent of the literature on this topic, they are not listed here (for reviews, see refs. 276–279).
- **Metabolic response to diet.** Individual variations in how the gut microbiota responds to dietary interventions might correlate with obesity risk and insulin sensitivity, paving the way for personalized dietary recommendations (for reviews, see refs. 280–282).
- **Microbial–host interaction genes.** Genetic variations that affect the interaction between gut microbes and the host can contribute to obesity and insulin resistance susceptibility, offering genetic markers for risk assessment.

Translating findings from animal models to humans is also challenging owing to biological differences between species. Genetic variations, diet, gut microbiota composition and environmental influences differ, making direct translation difficult. Animal models often oversimplify the complex human metabolic pathways and fail to account for the heterogeneity observed in human populations. This is one of the main reasons that findings from animal studies often remain unconfirmed in human studies and why data obtained solely from animal experiments must be cautiously interpreted.

Though many animal studies suggest that interventions targeting the gut microbiota and their metabolites hold promise in combating obesity and metabolic disorders, designing clinical trials to confirm these findings presents unique challenges. The gut microbiota exhibits substantial inter-individual variability, making it difficult to establish a standardized intervention with consistent effects across diverse populations[232]. Adding to the complexity is the fact that the gut microbiota is a highly dynamic and complex ecosystem that can be influenced by various factors, such as diet, medications, stress and other environmental factors, and that changes in the gut microbiota might take time to manifest or might fade over time[233].

The lack of standardization in the field of gut microbiota interventions extends to study design, sample collection and data analysis, making it incredibly difficult to compare and evaluate the effectiveness of these interventions.

There is considerable variability in the parameters of gut microbiota interventions. This variability includes the types of probiotics and prebiotics used, the dosages administered, and the duration and timing of the interventions. Different clinical and preclinical studies utilize various strains or combinations of strains, making it challenging to compare their efficacy. Furthermore, the optimal dosage and duration of interventions are not well established, leading to inconsistency in treatment regimens. The timing of intervention initiation and the route of administration also differ, introducing additional variability into the studies[234].

Data collection is another area where standardization is lacking. Variations in sample collection methods, such as stool collection techniques, storage conditions and transportation protocols, can affect the quality and consistency of gut microbiota data[235,236]. Additionally, the collection and reporting of metadata, including dietary information, lifestyle factors, medication use and clinical characteristics, are often inconsistent across studies[235,236]. The lack of standardized data collection procedures hampers the ability to accurately interpret and compare results.

Owing to their non-invasive collection method and sufficient biomass yield for analysis, faecal samples remain the primary source of material in most gut microbiota studies. Nevertheless, it is important to acknowledge the limitations when relying solely on faecal samples as the microbiota in faeces might not accurately represent the microbial communities at different locations within the intestine, leading to an incomplete understanding of the role and impact of gut microbiota on (human) health[237].

The gut microbiota varies along the length of the gastrointestinal tract with factors such as shifting environments, nutrient availability and distinct oxygen levels from the stomach to the large intestine[238]. Different microbial communities thrive in these varying conditions. Furthermore, the gut microbiota in the lumen of the intestine (faeces) might differ substantially from those residing closer to the mucosa, which lines the gut wall[239,240]. The mucosal layer is a dynamic interface where host–microorganism interactions occur. Microbes attached to the mucosa can have different roles and effects than those floating freely in the lumen[240]. Additionally, microbial communities in different parts of the gut might have distinct metabolic activities. For example, bacteria in the colon produce various metabolites through fermentation that can have systemic effects on host health[241].

Studying only faecal metabolites might not provide their complete picture, as they can be influenced by interactions between bacteria in various gut segments. Lastly, certain bacteria or metabolites can translocate from the gut lumen to other parts of the body, potentially affecting distant organs and systems[241]. Understanding the translocation dynamics and the specific microbial populations involved requires a more comprehensive sampling strategy beyond just faecal samples. However, so far, there are no clear biomarkers easily used in clinics to fully reflect gut permeability and its dynamics. As such, although faeces provide valuable insights, recognizing their limitations and addressing the challenges of accurately characterizing gut microbiota along the entire gastrointestinal tract is essential for a more holistic understanding of their roles in health and disease.

Moreover, analysing the gut microbiota presents its own challenges owing to the absence of standardized techniques and workflows. Different studies employ diverse approaches for profiling gut microbiota such as 16S rRNA gene sequencing, shotgun metagenomics or metatranscriptomics. Each method has its own strengths and limitations, and the choice of technique can affect the accuracy and comprehensiveness of the results. The functional metagenomic approach using shotgun sequencing and biochemical interpretation has emerged as a powerful tool in microbiome research through the identification of functional bacterial genes and pathways that contribute to various physiological processes[242], but even this technique has its limitations. Besides the high cost, the complexity of data interpretation and functional annotation challenges, shotgun metagenomic sequencing only provides information about the presence of functional genes but might not fully capture information about gene expression and regulation[243]. Furthermore, no standardized bioinformatics pipeline exists for processing and analysing gut microbiota data. Varying approaches for quality control, taxonomic assignment and statistical analysis can lead to discrepancies and difficulties in comparing results across studies[235].

Conclusions

Over the course of the last two decades, substantial advancements have been made in understanding the relationship between gut microbiota and human health. Initially, the field relied on clinical observations. However, as research progressed, scientists began adopting more mechanistic approaches to delve deeper into the underlying mechanisms at play. As a result of these efforts, the field has evolved to establish, as much as possible, irrefutable causal links between gut microbiota and health outcomes. This means that some researchers have been able to demonstrate that certain changes in the gut microbiota composition directly led to specific health effects. For example, researchers have found that alterations in the gut microbiota can contribute to conditions such as obesity, diabetes, inflammatory bowel disease and even mental health disorders.

However, despite these marked strides, it is important to acknowledge that numerous studies still mistakenly conclude direct causal relationships when they only demonstrate correlations. In other words, they identify a relationship between the gut microbiota and certain health outcomes but do not establish a cause-and-effect relationship. Moving from correlation to causality remains a crucial and necessary step in the field[244]. By accurately determining the causal links between specific gut microbiota changes and health effects, researchers can better design potential interventions. These interventions might involve manipulating the gut microbiota through various means or utilizing specific active compounds to achieve desired health outcomes. Developing specific interventions that target adipose tissue by influencing the gut microbiota or their metabolites continues to pose challenges. Fortunately, thanks to the concerted efforts of scientists and the advancements in omics analysis, the scientific community is gradually progressing towards personalized medicine. This emerging field aims to tailor medical treatments and nutritional approaches to individual patients based on their unique gut microbiota composition and other personal factors. The microbiome era, with its focus on understanding and harnessing the potential of the gut microbiota, including its role in the different adipose tissues, is undeniably a crucial component of this paradigm shift in the future of medicine and health care.

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References

1. Valenzuela, P. L. et al. Obesity and the risk of cardiometabolic diseases. *Nat. Rev. Cardiol.* **20**, 475–494 (2023).
2. Saha, A., Kolonin, M. G. & DiGiovanni, J. Obesity and prostate cancer — microenvironmental roles of adipose tissue. *Nat. Rev. Urol.* **20**, 579–596 (2023).
3. de Vos, W. M., Tilg, H., Van Hul, M. & Cani, P. D. Gut microbiome and health: mechanistic insights. *Gut* **71**, 1020–1032 (2022).
4. Van Hul, M. & Cani, P. D. The gut microbiota in obesity and weight management: microbes as friends or foe. *Nat. Rev. Endocrinol.* **19**, 258–271 (2023).
5. Lafontan, M. Historical perspectives in fat cell biology: the fat cell as a model for the investigation of hormonal and metabolic pathways. *Am. J. Physiol. Cell Physiol.* **302**, C327–C359 (2012).
6. Hammarstedt, A., Gogg, S., Hedjazifar, S., Nerstedt, A. & Smith, U. Impaired adipogenesis and dysfunctional adipose tissue in human hypertrophic obesity. *Physiol. Rev.* **98**, 1911–1941 (2018).
7. White, U., Beyl, R. A. & Ravussin, E. A higher proportion of small adipocytes is associated with increased visceral and ectopic lipid accumulation during weight gain in response to overfeeding in men. *Int. J. Obes.* **46**, 1560–1563 (2022).
8. White, U. & Ravussin, E. Dynamics of adipose tissue turnover in human metabolic health and disease. *Diabetologia* **62**, 17–23 (2019).
9. Koenen, M., Hill, M. A., Cohen, P. & Sowers, J. R. Obesity, adipose tissue and vascular dysfunction. *Circ. Res.* **128**, 951–968 (2021).
10. Longo, M. et al. Adipose tissue dysfunction as determinant of obesity-associated metabolic complications. *Int. J. Mol. Sci.* **20**, 2358 (2019).
11. Kahn, C. R., Wang, G. & Lee, K. Y. Altered adipose tissue and adipocyte function in the pathogenesis of metabolic syndrome. *J. Clin. Invest.* **129**, 3990–4000 (2019).
12. Karpe, F. & Pinnick, K. E. Biology of upper-body and lower-body adipose tissue — link to whole-body phenotypes. *Nat. Rev. Endocrinol.* **11**, 90–100 (2015).
13. Zhang, M., Hu, T., Zhang, S. & Zhou, L. Associations of different adipose tissue depots with insulin resistance: a systematic review and meta-analysis of observational studies. *Sci. Rep.* **5**, 18495 (2015).
14. Tchkonia, T. et al. Mechanisms and metabolic implications of regional differences among fat depots. *Cell Metab.* **17**, 644–656 (2013).
15. McLaughlin, T., Lamendola, C., Liu, A. & Abbasi, F. Preferential fat deposition in subcutaneous versus visceral depots is associated with insulin sensitivity. *J. Clin. Endocrinol. Metab.* **96**, E1756–1760 (2011).
16. Klein, S. et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. *N. Engl. J. Med.* **350**, 2549–2557 (2004).
17. Tran, T. T., Yamamoto, Y., Gesta, S. & Kahn, C. R. Beneficial effects of subcutaneous fat transplantation on metabolism. *Cell Metab.* **7**, 410–420 (2008).
18. Cypess, A. M. Reassessing human adipose tissue. *N. Engl. J. Med.* **386**, 768–779 (2022).
19. Luong, Q., Huang, J. & Lee, K. Y. Deciphering white adipose tissue heterogeneity. *Biology* **8**, 23 (2019).
20. Iacobellis, G. Epicardial adipose tissue in contemporary cardiology. *Nat. Rev. Cardiol.* **19**, 593–606 (2022).
21. Zhang, H. et al. Characteristics of mesenteric adipose tissue attached to different intestinal segments and their roles in immune regulation. *Am. J. Physiol. Gastrointest. Liver Physiol.* **322**, G310–G326 (2022).
22. Wu, Z. et al. Mesenteric adipose tissue contributes to intestinal barrier integrity and protects against nonalcoholic fatty liver disease in mice. *Am. J. Physiol. Gastrointest. Liver Physiol.* **315**, G659–G670 (2018).
23. Yu, Z., Wang, Y., Yu, Z., Lu, M. & Xu, B. Crosstalk between adipose tissue and the microbiota-gut-brain axis in metabolic diseases. *Int. J. Biol. Sci.* **18**, 1706–1723 (2022).
24. Virtanen, K. A. et al. Functional brown adipose tissue in healthy adults. *N. Engl. J. Med.* **360**, 1518–1525 (2009).
25. Jung, S. M., Sanchez-Gurmaches, J. & Guertin, D. A. Brown adipose tissue development and metabolism. *Handb. Exp. Pharmacol.* **251**, 3–36 (2019).
26. Yang, F. T. & Stanford, K. I. Batokines: mediators of inter-tissue communication (a mini-review). *Curr. Obes. Rep.* **11**, 1–9 (2022).
27. Scheele, C. & Wolfrum, C. Brown adipose crosstalk in tissue plasticity and human metabolism. *Endocr. Rev.* **41**, 53–65 (2020).

28. Kajimura, S. et al. Regulation of the brown and white fat gene programs through a PRDM16/CtBP transcriptional complex. *Genes Dev.* **22**, 1397–1409 (2008).
29. Seale, P. et al. PRDM16 controls a brown fat/skeletal muscle switch. *Nature* **454**, 961–967 (2008).
30. Timmons, J. A. et al. Myogenic gene expression signature establishes that brown and white adipocytes originate from distinct cell lineages. *Proc. Natl Acad. Sci. USA* **104**, 4401–4406 (2007).
31. Sanchez-Gurmaches, J. & Guertin, D. A. Adipocytes arise from multiple lineages that are heterogeneously and dynamically distributed. *Nat. Commun.* **5**, 4099 (2014).
32. Schulz, T. J. et al. Identification of inducible brown adipocyte progenitors residing in skeletal muscle and white fat. *Proc. Natl Acad. Sci. USA* **108**, 143–148 (2011).
33. Yang Loureiro, Z. et al. Wnt signaling preserves progenitor cell multipotency during adipose tissue development. *Nat. Metab.* **5**, 1014–1028 (2023).
34. Palani, N. P. et al. Adipogenic and SWAT cells separate from a common progenitor in human brown and white adipose depots. *Nat. Metab.* **5**, 996–1013 (2023).
35. Demine, S., Renard, P. & Arnould, T. Mitochondrial uncoupling: a key controller of biological processes in physiology and diseases. *Cells* **8**, 795 (2019).
36. Kalinovich, A. V., de Jong, J. M., Cannon, B. & Nedergaard, J. UCP1 in adipose tissues: two steps to full browning. *Biochimie* **134**, 127–137 (2017).
37. Lam, Y. Y. & Ravussin, E. Analysis of energy metabolism in humans: a review of methodologies. *Mol. Metab.* **5**, 1057–1071 (2016).
38. Cani, P. D. et al. Microbial regulation of organismal energy homeostasis. *Nat. Metab.* **1**, 34–46 (2019).
39. Buchholz, A. C. & Schoeller, D. A. Is a calorie a calorie? *Am. J. Clin. Nutr.* **79**, 899S–906S (2004).
40. Cani, P. D. & Van Hul, M. Mediterranean diet, gut microbiota and health: when age and calories do not add up! *Gut* **69**, 1167–1168 (2020).
41. Westerterp, K. R. Perception, passive overfeeding and energy metabolism. *Physiol. Behav.* **89**, 62–65 (2006).
42. Swaminathan, R. et al. Thermic effect of feeding carbohydrate, fat, protein and mixed meal in lean and obese subjects. *Am. J. Clin. Nutr.* **42**, 177–181 (1985).
43. Calcagno, M. et al. The thermic effect of food: a review. *J. Am. Coll. Nutr.* **38**, 547–551 (2019).
44. Du, S., Rajjo, T., Santosa, S. & Jensen, M. D. The thermic effect of food is reduced in older adults. *Horm. Metab. Res.* **46**, 365–369 (2014).
45. Binns, A., Gray, M. & Di Brezzo, R. Thermic effect of food, exercise, and total energy expenditure in active females. *J. Sci. Med. Sport* **18**, 204–208 (2015).
46. Halton, T. L. & Hu, F. B. The effects of high protein diets on thermogenesis, satiety and weight loss: a critical review. *J. Am. Coll. Nutr.* **23**, 373–385 (2004).
47. Macdonald, I. A. A review of recent evidence relating to sugars, insulin resistance and diabetes. *Eur. J. Nutr.* **55**, 17–23 (2016).
48. Fuglsang-Nielsen, R. et al. Effects of whey protein and dietary fiber intake on insulin sensitivity, body composition, energy expenditure, blood pressure, and appetite in subjects with abdominal obesity. *Eur. J. Clin. Nutr.* **75**, 611–619 (2021).
49. Meslier, V. et al. Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. *Gut* **69**, 1258–1268 (2020).
50. Reynolds, A. N., Akerman, A. P. & Mann, J. Dietary fibre and whole grains in diabetes management: systematic review and meta-analyses. *PLoS Med.* **17**, e1003053 (2020).
51. Thyfault, J. P. & Bergouignan, A. Exercise and metabolic health: beyond skeletal muscle. *Diabetologia* **63**, 1464–1474 (2020).
52. Richter, E. A. & Ruderman, N. B. AMPK and the biochemistry of exercise: implications for human health and disease. *Biochem. J.* **418**, 261–275 (2009).
53. Liang, H. & Ward, W. F. PGC-1α: a key regulator of energy metabolism. *Adv. Physiol. Educ.* **30**, 145–151 (2006).
54. Stanford, K. I. et al. 12,13-DiHOME: an exercise-induced lipokine that increases skeletal muscle fatty acid uptake. *Cell Metab.* **27**, 1111–1120.e3 (2018).
55. Lynes, M. D. et al. The cold-induced lipokine 12,13-diHOME promotes fatty acid transport into brown adipose tissue. *Nat. Med.* **23**, 631–637 (2017).
56. Reutrakul, S. & Van Cauter, E. Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes. *Metabolism* **84**, 56–66 (2018).
57. Spiegel, K., Knutson, K., Leproult, R., Tasali, E. & Van Cauter, E. Sleep loss: a novel risk factor for insulin resistance and type 2 diabetes. *J. Appl. Physiol.* **99**, 2008–2019 (2005).
58. Zhu, B., Shi, C., Park, C. G., Zhao, X. & Reutrakul, S. Effects of sleep restriction on metabolism-related parameters in healthy adults: a comprehensive review and meta-analysis of randomized controlled trials. *Sleep Med. Rev.* **45**, 18–30 (2019).
59. Soltanieh, S., Solgi, S., Ansari, M., Santos, H. O. & Abbasi, B. Effect of sleep duration on dietary intake, desire to eat, measures of food intake and metabolic hormones: a systematic review of clinical trials. *Clin. Nutr. ESPEN* **45**, 55–65 (2021).
60. Frank, S. et al. Diet and sleep physiology: public health and clinical implications. *Front. Neurol.* **8**, 393 (2017).
61. Cooper, C. B., Neufeld, E. V., Dolezal, B. A. & Martin, J. L. Sleep deprivation and obesity in adults: a brief narrative review. *BMJ Open Sport Exerc. Med.* **4**, e000392 (2018).
62. Shan, Z. et al. Sleep duration and risk of type 2 diabetes: a meta-analysis of prospective studies. *Diabetes Care* **38**, 529–537 (2015).
63. Ayas, N. T. et al. A prospective study of self-reported sleep duration and incident diabetes in women. *Diabetes Care* **26**, 380–384 (2003).
64. Smith, S. M. & Vale, W. W. The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. *Dialogues Clin. Neurosci.* **8**, 383–395 (2006).
65. Hirotsu, C., Tufik, S. & Andersen, M. L. Interactions between sleep, stress, and metabolism: from physiological to pathological conditions. *Sleep Sci.* **8**, 143–152 (2015).
66. Sato, F., Kohsaka, A., Bhawal, U. K. & Muragaki, Y. Potential roles of *Dec* and *Bmal1* genes in interconnecting circadian clock and energy metabolism. *Int. J. Mol. Sci.* **19**, 781 (2018).
67. Nowak, N., Rawleigh, A. & Brown, S. A. Circadian clocks, sleep, and metabolism. *Adv. Exp. Med. Biol.* **1344**, 21–42 (2021).
68. Broussard, J. L., Ehrmann, D. A., Van Cauter, E., Tasali, E. & Brady, M. J. Impaired insulin signaling in human adipocytes after experimental sleep restriction: a randomized, crossover study. *Ann. Intern. Med.* **157**, 549–557 (2012).
69. Sweeney, E. L., Jeromson, S., Hamilton, D. L., Brooks, N. E. & Walshe, I. H. Skeletal muscle insulin signaling and whole-body glucose metabolism following acute sleep restriction in healthy males. *Physiol. Rep.* **5**, e13498 (2017).
70. Schmid, S. M., Hallschmid, M., Jauch-Chara, K., Born, J. & Schultes, B. A single night of sleep deprivation increases ghrelin levels and feelings of hunger in normal-weight healthy men. *J. Sleep Res.* **17**, 331–334 (2008).
71. Liu, S., Wang, X., Zheng, Q., Gao, L. & Sun, Q. Sleep deprivation and central appetite regulation. *Nutrients* **14**, 5196 (2022).
72. van Egmond, L. T. et al. Effects of acute sleep loss on leptin, ghrelin, and adiponectin in adults with healthy weight and obesity: a laboratory study. *Obesity* **31**, 635–641 (2023).
73. Colangeli, L. et al. The crosstalk between gut microbiota and white adipose tissue mitochondria in obesity. *Nutrients* **15**, 1723 (2023).
74. Backhed, F., Manchester, J. K., Semenkovich, C. F. & Gordon, J. I. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc. Natl Acad. Sci. USA* **104**, 979–984 (2007).
75. Rabot, S. et al. Germ-free C57BL/6J mice are resistant to high-fat-diet-induced insulin resistance and have altered cholesterol metabolism. *FASEB J.* **24**, 4948–4959 (2010).
76. Backhed, F. et al. The gut microbiota as an environmental factor that regulates fat storage. *Proc. Natl Acad. Sci. USA* **101**, 15718–15723 (2004).
77. Muccioli, G. et al. The endocannabinoid system links gut microbiota to adipogenesis. *Mol. Syst. Biol.* **6**, 392 (2010).
78. Cani, P. D. et al. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* **57**, 1470–1481 (2008).
79. Chevalier, C. et al. Gut microbiota orchestrates energy homeostasis during cold. *Cell* **163**, 1360–1374 (2015).
80. Geurts, L. et al. Adipose tissue NAPE-PLD controls fat mass development by altering the browning process and gut microbiota. *Nat. Commun.* **6**, 6495 (2015).
81. Suarez-Zamorano, N. et al. Microbiota depletion promotes browning of white adipose tissue and reduces obesity. *Nat. Med.* **21**, 1497–1501 (2015).
82. Gibson, G. R. et al. Expert consensus document: the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat. Rev. Gastroenterol. Hepatol.* **14**, 491–502 (2017).
83. Hill, C. et al. Expert consensus document: the International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat. Rev. Gastroenterol. Hepatol.* **11**, 506–514 (2014).
84. Salminen, S. et al. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics. *Nat. Rev. Gastroenterol. Hepatol.* **18**, 649–667 (2021).
85. Aguilar-Toala, J. E. et al. Postbiotics — when simplification fails to clarify. *Nat. Rev. Gastroenterol. Hepatol.* **18**, 825–826 (2021).
86. Vinderola, G., Sanders, M. E. & Salminen, S. The concept of postbiotics. *Foods* **11**, 1077 (2022).
87. Rinott, E. et al. Effects of diet-modulated autologous fecal microbiota transplantation on weight regain. *Gastroenterology* **160**, 158–173.e10 (2021).
88. Wolters, M. et al. Dietary fat, the gut microbiota, and metabolic health — a systematic review conducted within the MyNewGut project. *Clin. Nutr.* **38**, 2504–2520 (2019).
89. Mocanu, V. et al. Fecal microbial transplantation and fiber supplementation in patients with severe obesity and metabolic syndrome: a randomized double-blind, placebo-controlled phase 2 trial. *Nat. Med.* **27**, 1272–1279 (2021).
90. Rastall, R. A. et al. Structure and function of non-digestible carbohydrates in the gut microbiome. *Benef. Microbes* **13**, 95–168 (2022).
91. Bartlett, A. & Kleiner, M. Dietary protein and the intestinal microbiota: an understudied relationship. *iScience* **25**, 105313 (2022).
92. Suriano, F. et al. Fat and not sugar as the determining factor for gut microbiota changes, obesity, and related metabolic disorders in mice. *Am. J. Physiol. Endocrinol. Metab.* **324**, E85–E96 (2023).
93. Allen, J. M. et al. Exercise alters gut microbiota composition and function in lean and obese humans. *Med. Sci. Sports Exerc.* **50**, 747–757 (2018).
94. Sun, J., Fang, D., Wang, Z. & Liu, Y. Sleep deprivation and gut microbiota dysbiosis: current understandings and implications. *Int J. Mol. Sci.* **24**, 9603 (2023).
95. Yoon, J. C. et al. Peroxisome proliferator-activated receptor γ target gene encoding a novel angiopoietin-related protein associated with adipose differentiation. *Mol. Cell Biol.* **20**, 5343–5349 (2000).
96. Kersten, S. et al. Peroxisome proliferator-activated receptor α mediates the adaptive response to fasting. *J. Clin. Invest.* **103**, 1489–1498 (1999).
97. Wang, H. & Eckel, R. H. Lipoprotein lipase: from gene to obesity. *Am. J. Physiol. Endocrinol. Metab.* **297**, E271–288 (2009).
98. Fleissner, C. K. et al. Absence of intestinal microbiota does not protect mice from diet-induced obesity. *Br. J. Nutr.* **104**, 919–929 (2010).

99. Kubeck, R. et al. Dietary fat and gut microbiota interactions determine diet-induced obesity in mice. *Mol. Metab.* **5**, 1162–1174 (2016).
100. Moretti, C. H. et al. Germ-free mice are not protected against diet-induced obesity and metabolic dysfunction. *Acta Physiol.* **231**, e13581 (2021).
101. Jacouton, E. et al. *Lactobacillus rhamnosus* CNCMI-4317 modulates Fiaf/Angptl4 in intestinal epithelial cells and circulating level in mice. *PLoS One* **10**, e0138880 (2015).
102. Kim, H. K. et al. Hypothalamic Angptl4/Fiaf is a novel regulator of food intake and body weight. *Diabetes* **59**, 2772–2780 (2010).
103. Slavin, J. Fiber and prebiotics: mechanisms and health benefits. *Nutrients* **5**, 1417–1435 (2013).
104. Roberfroid, M. et al. Prebiotic effects: metabolic and health benefits. *Br. J. Nutr.* **104**, S1–S63 (2010).
105. Nicholson, J. K. et al. Host-gut microbiota metabolic interactions. *Science* **336**, 1262–1267 (2012).
106. Cronin, P., Joyce, S. A., O'Toole, P. W. & O'Connor, E. M. Dietary fibre modulates the gut microbiota. *Nutrients* **13**, 1655 (2021).
107. Bergman, E. N. Energy contributions of volatile fatty acids from the gastrointestinal tract in various species. *Physiol. Rev.* **70**, 567–590 (1990).
108. Blaak, E. E. et al. Short chain fatty acids in human gut and metabolic health. *Benef. Microbes* **11**, 411–455 (2020).
109. Canfora, E. E., Jocken, J. W. & Blaak, E. E. Short-chain fatty acids in control of body weight and insulin sensitivity. *Nat. Rev. Endocrinol.* **11**, 577–591 (2015).
110. Dalile, B., Van Oudenhove, L., Vervliet, B. & Verbeke, K. The role of short-chain fatty acids in microbiota-gut-brain communication. *Nat. Rev. Gastroenterol. Hepatol.* **16**, 461–478 (2019).
111. Sanna, S. et al. Causal relationships among the gut microbiome, short-chain fatty acids and metabolic diseases. *Nat. Genet.* **51**, 600–605 (2019).
112. Anachad, O., Taouil, A., Taha, W., Bennis, F. & Chegdani, F. The implication of short-chain fatty acids in obesity and diabetes. *Microbiol. Insights* **16**, 11786361231162720 (2023).
113. Rastelli, M., Cani, P. D. & Knauf, C. The gut microbiome influences host endocrine functions. *Endocr. Rev.* **40**, 1271–1284 (2019).
114. Chambers, E. S. et al. Acute oral sodium propionate supplementation raises resting energy expenditure and lipid oxidation in fasted humans. *Diabetes Obes. Metab.* **20**, 1034–1039 (2018).
115. Chambers, E. S., Preston, T., Frost, G. & Morrison, D. J. Role of gut microbiota-generated short-chain fatty acids in metabolic and cardiovascular health. *Curr. Nutr. Rep.* **7**, 198–206 (2018).
116. Chambers, E. S. et al. Dietary supplementation with inulin-propionate ester or inulin improves insulin sensitivity in adults with overweight and obesity with distinct effects on the gut microbiota, plasma metabolome and systemic inflammatory responses: a randomised cross-over trial. *Gut* **68**, 1430–1438 (2019).
117. Byrne, C. S. et al. Effects of inulin propionate ester incorporated into palatable food products on appetite and resting energy expenditure: a randomised crossover study. *Nutrients* **11**, 861 (2019).
118. Hong, Y. H. et al. Acetate and propionate short chain fatty acids stimulate adipogenesis via GPCR43. *Endocrinology* **146**, 5092–5099 (2005).
119. Dewulf, E. et al. Inulin-type fructans with prebiotic properties counteract GPR43 overexpression and PPARγ-related adipogenesis in the white adipose tissue of high-fat diet-fed mice. *J. Nutr. Biochem.* **22**, 712–722 (2011).
120. Dewulf, E. M. et al. Evaluation of the relationship between GPR43 and adiposity in human. *Nutr. Metab.* **10**, 11 (2013).
121. Yu, H., Li, R., Huang, H., Yao, R. & Shen, S. Short-chain fatty acids enhance the lipid accumulation of 3T3-L1 cells by modulating the expression of enzymes of fatty acid metabolism. *Lipids* **53**, 77–84 (2018).
122. May, K. S. & den Hartigh, L. J. Modulation of adipocyte metabolism by microbial short-chain fatty acids. *Nutrients* **13**, 3666 (2021).
123. Hu, J. et al. Short-chain fatty acid acetate stimulates adipogenesis and mitochondrial biogenesis via GPR43 in brown adipocytes. *Endocrinology* **157**, 1881–1894 (2016).
124. Li, Z. et al. Butyrate reduces appetite and activates brown adipose tissue via the gut-brain neural circuit. *Gut* **67**, 1269–1279 (2018).
125. Sharma, M., Li, Y., Stoll, M. L. & Tollefsbol, T. O. The epigenetic connection between the gut microbiome in obesity and diabetes. *Front. Genet.* **10**, 1329 (2019).
126. Hotamisligil, G. S. Inflammation and metabolic disorders. *Nature* **444**, 860–867 (2006).
127. Cani, P. D. et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* **56**, 1761–1772 (2007).
128. Cani, P. D. Human gut microbiome: hopes, threats and promises. *Gut* **67**, 1716–1725 (2018).
129. Regnier, M., Van Hul, M., Knauf, C. & Cani, P. D. Gut microbiome, endocrine control of gut barrier function and metabolic diseases. *J. Endocrinol.* **248**, R67–R82 (2021).
130. Leclercq, S. et al. Intestinal permeability, gut-bacterial dysbiosis, and behavioral markers of alcohol-dependence severity. *Proc. Natl Acad. Sci. USA* **111**, E4485–E4493 (2014).
131. Brun, P. et al. Increased intestinal permeability in obese mice: new evidence in the pathogenesis of nonalcoholic steatohepatitis. *Am. J. Physiol. Gastrointest. Liver Physiol.* **292**, G518–G525 (2007).
132. Cani, P. D. et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* **58**, 1091–1103 (2009).
133. Suriano, F. et al. Novel insights into the genetically obese (ob/ob) and diabetic (db/db) mice: two sides of the same coin. *Microbiome* **9**, 147 (2021).
134. Thaiss, C. A. et al. Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection. *Science* **359**, 1376–1383 (2018).
135. Chassaing, B. et al. Lack of soluble fiber drives diet-induced adiposity in mice. *Am. J. Physiol. Gastrointest. Liver Physiol.* **309**, G528-41 (2015).
136. Everard, A. et al. Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity. *Proc. Natl Acad. Sci. USA* **110**, 9066–9071 (2013).
137. Everard, A. et al. Microbiome of prebiotic-treated mice reveals novel targets involved in host response during obesity. *ISME J.* **8**, 2116–2130 (2014).
138. Guo, X. et al. High fat diet alters gut microbiota and the expression of paneth cell-antimicrobial peptides preceding changes of circulating inflammatory cytokines. *Mediators Inflamm.* **2017**, 9474896 (2017).
139. Paone, P. & Cani, P. D. Mucus barrier, mucins and gut microbiota: the expected slimy partners? *Gut* **69**, 2232–2243 (2020).
140. Caesar, R. et al. Gut-derived lipopolysaccharide augments adipose macrophage accumulation but is not essential for impaired glucose or insulin tolerance in mice. *Gut* **61**, 1701–1707 (2012).
141. Hersoug, L. G., Moller, P. & Loft, S. Gut microbiota-derived lipopolysaccharide uptake and trafficking to adipose tissue: implications for inflammation and obesity. *Obes. Rev.* **17**, 297–312 (2016).
142. Chung, S. et al. Preadipocytes mediate lipopolysaccharide-induced inflammation and insulin resistance in primary cultures of newly differentiated human adipocytes. *Endocrinology* **147**, 5340–5351 (2006).
143. Poulain-Godefroy, O. & Froguel, P. Preadipocyte response and impairment of differentiation in an inflammatory environment. *Biochem. Biophys. Res. Commun.* **356**, 662–667 (2007).
144. Poulain-Godefroy, O., Lecoeur, C., Pattou, F., Fruhbeck, G. & Froguel, P. Inflammation is associated with a decrease of lipogenic factors in omental fat in women. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **295**, R1–R7 (2008).
145. Cawthorn, W. P., Heyd, F., Hegyi, K. & Sethi, J. K. Tumour necrosis factor-α inhibits adipogenesis via a β-catenin/TCF4(TCF7L2)-dependent pathway. *Cell Death Differ.* **14**, 1361–1373 (2007).
146. Luo, X. et al. β-Catenin protein utilized by tumour necrosis factor-alpha in porcine preadipocytes to suppress differentiation. *BMB Rep.* **42**, 338–343 (2009).
147. Geurts, L. et al. Altered gut microbiota and endocannabinoid system tone in obese and diabetic leptin-resistant mice: impact on apelin regulation in adipose tissue. *Front. Microbiol.* **2**, 149 (2011).
148. Than, A. et al. Apelin inhibits adipogenesis and lipolysis through distinct molecular pathways. *Mol. Cell Endocrinol.* **362**, 227–241 (2012).
149. Zhao, M. & Chen, X. Effect of lipopolysaccharides on adipogenic potential and premature senescence of adipocyte progenitors. *Am. J. Physiol. Endocrinol. Metab.* **309**, E334–344 (2015).
150. Chang, C. C. et al. Lipopolysaccharide promoted proliferation and adipogenesis of preadipocytes through JAK/STAT and AMPK-regulated cPLA2 expression. *Int. J. Med. Sci.* **16**, 167–179 (2019).
151. Luche, E. et al. Metabolic endotoxemia directly increases the proliferation of adipocyte precursors at the onset of metabolic diseases through a CD14-dependent mechanism. *Mol. Metab.* **2**, 281–291 (2013).
152. Ding, S. et al. High-fat diet: bacteria interactions promote intestinal inflammation which precedes and correlates with obesity and insulin resistance in mouse. *PLoS One* **5**, e12191 (2010).
153. Anhê, F. F., Barra, N. G., Cavallari, J. F., Henriksbo, B. D. & Schertzer, J. D. Metabolic endotoxemia is dictated by the type of lipopolysaccharide. *Cell Rep.* **36**, 109691 (2021).
154. Moreno-Navarrete, J. M. et al. Lysozyme is a component of the innate immune system linked to obesity associated-chronic low-grade inflammation and altered glucose tolerance. *Clin. Nutr.* **40**, 1420–1429 (2021).
155. Chi, W. et al. Bacterial peptidoglycan stimulates adipocyte lipolysis via NOD1. *PLoS One* **9**, e97675 (2014).
156. Foley, K. P. et al. Inflammation promotes adipocyte lipolysis via IRE1 kinase. *J. Biol. Chem.* **296**, 100440 (2021).
157. Schertzer, J. D. et al. NOD1 activators link innate immunity to insulin resistance. *Diabetes* **60**, 2206–2215 (2011).
158. Gao, H. et al. Accumulation of microbial DNAs promotes to islet inflammation and beta cell abnormalities in obesity in mice. *Nat. Commun.* **13**, 565 (2022).
159. Jialal, I., Kaur, H. & Devaraj, S. Toll-like receptor status in obesity and metabolic syndrome: a translational perspective. *J. Clin. Endocrinol. Metab.* **99**, 39–48 (2014).
160. Guerrero-Romero, F. et al. Association between the expression of TLR4, TLR2, and MyD88 with low-grade chronic inflammation in individuals with metabolically healthy obesity. *Mol. Biol. Rep.* **50**, 4723–4728 (2023).
161. Vijay-Kumar, M. et al. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science* **328**, 228–231 (2010).
162. Guadagnini, D. et al. Microbiota determines insulin sensitivity in TLR2-KO mice. *Life Sci.* **234**, 116793 (2019).
163. Denou, E. et al. Defective NOD2 peptidoglycan sensing promotes diet-induced inflammation, dysbiosis, and insulin resistance. *EMBO Mol. Med.* **7**, 259–274 (2015).
164. Rojas, I. Y. et al. Kynurenine-induced aryl hydrocarbon receptor signaling in mice causes body mass gain, liver steatosis, and hyperglycemia. *Obesity* **29**, 337–349 (2021).
165. Favennec, M. et al. The kynurenine pathway is activated in human obesity and shifted toward kynurenine monooxygenase activation. *Obesity* **23**, 2066–2074 (2015).

166. Vujkovic-Cvijin, I. et al. Dysbiosis of the gut microbiota is associated with HIV disease progression and tryptophan catabolism. *Sci. Transl. Med.* **5**, 193ra91 (2013).
167. Alexander, D. L., Ganem, L. G., Fernandez-Salguero, P., Gonzalez, F. & Jefcoate, C. R. Aryl-hydrocarbon receptor is an inhibitory regulator of lipid synthesis and of commitment to adipogenesis. *J. Cell Sci.* **111**, 3311–3322 (1998).
168. Dou, H. et al. Aryl hydrocarbon receptor (AhR) regulates adipocyte differentiation by assembling CRL4B ubiquitin ligase to target PPARγ for proteasomal degradation. *J. Biol. Chem.* **294**, 18504–18515 (2019).
169. Agudelo, L. Z. et al. Kynurenic acid and Gpr35 regulate adipose tissue energy homeostasis and inflammation. *Cell Metab.* **27**, 378–392.e5 (2018).
170. Laurans, L. et al. Genetic deficiency of indoleamine 2,3-dioxygenase promotes gut microbiota-mediated metabolic health. *Nat. Med.* **24**, 1113–1120 (2018).
171. Huang, T. et al. Adipocyte-derived kynurenine promotes obesity and insulin resistance by activating the AhR/STAT3/IL-6 signaling. *Nat. Commun.* **13**, 3489 (2022).
172. Virtue, A. T. et al. The gut microbiota regulates white adipose tissue inflammation and obesity via a family of microRNAs. *Sci. Transl. Med.* **11**, eaav1892 (2019).
173. Park, J. et al. Bioactive lipids and their derivatives in biomedical applications. *Biomol. Ther.* **29**, 465–482 (2021).
174. Ayub, M., Jin, H. K. & Bae, J. S. Novelty of sphingolipids in the central nervous system physiology and disease: focusing on the sphingolipid hypothesis of neuroinflammation and neurodegeneration. *Int. J. Mol. Sci.* **22**, 7353 (2021).
175. Leuti, A. et al. Bioactive lipids, inflammation and chronic diseases. *Adv. Drug Deliv. Rev.* **159**, 133–169 (2020).
176. Cani, P. D. et al. Endocannabinoids — at the crossroads between the gut microbiota and host metabolism. *Nat. Rev. Endocrinol.* **12**, 133–143 (2016).
177. Russo, R. et al. Gut-brain axis: role of lipids in the regulation of inflammation, pain and CNS diseases. *Curr. Med. Chem.* **25**, 3930–3952 (2018).
178. Lavelle, A. & Sokol, H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. *Nat. Rev. Gastroenterol. Hepatol.* **17**, 223–237 (2020).
179. Collins, S. L., Stine, J. G., Bisanz, J. E., Okafor, C. D. & Patterson, A. D. Bile acids and the gut microbiota: metabolic interactions and impacts on disease. *Nat. Rev. Microbiol.* **21**, 236–247 (2023).
180. Lefort, C. & Cani, P. D. The liver under the spotlight: bile acids and oxysterols as pivotal actors controlling metabolism. *Cells* **10**, 400 (2021).
181. Dawson, P. A. & Karpen, S. J. Intestinal transport and metabolism of bile acids. *J. Lipid Res.* **56**, 1085–1099 (2015).
182. Ahmad, T. R. & Haeusler, R. A. Bile acids in glucose metabolism and insulin signalling — mechanisms and research needs. *Nat. Rev. Endocrinol.* **15**, 701–712 (2019).
183. Chen, X., Lou, G., Meng, Z. & Huang, W. TGR5: a novel target for weight maintenance and glucose metabolism. *Exp. Diabetes Res.* **2011**, 853501 (2011).
184. Velazquez-Villegas, L. A. et al. TGR5 signalling promotes mitochondrial fission and beige remodelling of white adipose tissue. *Nat. Commun.* **9**, 245 (2018).
185. Broeders, E. P. et al. The bile acid chenodeoxycholic acid increases human brown adipose tissue activity. *Cell Metab.* **22**, 418–426 (2015).
186. Pellicciari, R. et al. Discovery of 6α-ethyl-23(S)-methylcholic acid (S-EMCA, INT-777) as a potent and selective agonist for the TGR5 receptor, a novel target for diabesity. *J. Med. Chem.* **52**, 7958–7961 (2009).
187. Murakami, M. et al. Incretin secretion stimulated by ursodeoxycholic acid in healthy subjects. *Springerplus* **2**, 20 (2013).
188. Bala, V. et al. Release of GLP-1 and PYY in response to the activation of G protein-coupled bile acid receptor TGR5 is mediated by Epac/PLC-epsilon pathway and modulated by endogenous H2S. *Front. Physiol.* **5**, 420 (2014).
189. Devane, W. A., Dysarz, F. A. III, Johnson, M. R., Melvin, L. S. & Howlett, A. C. Determination and characterization of a cannabinoid receptor in rat brain. *Mol. Pharmacol.* **34**, 605–613 (1988).
190. Munro, S., Thomas, K. L. & Abu-Shaar, M. Molecular characterization of a peripheral receptor for cannabinoids. *Nature* **365**, 61–65 (1993).
191. D'Eon, T. M. et al. The role of adipocyte insulin resistance in the pathogenesis of obesity-related elevations in endocannabinoids. *Diabetes* **57**, 1262–1268 (2008).
192. Starowicz, K. M. et al. Endocannabinoid dysregulation in the pancreas and adipose tissue of mice fed with a high-fat diet. *Obesity* **16**, 553–565 (2008).
193. Sarzani, R. et al. Altered pattern of cannabinoid type 1 receptor expression in adipose tissue of dysmetabolic and overweight patients. *Metabolism* **58**, 361–367 (2009).
194. Gasperi, V. et al. Endocannabinoids in adipocytes during differentiation and their role in glucose uptake. *Cell Mol. Life Sci.* **64**, 219–229 (2007).
195. Everard, A. et al. Intestinal epithelial N-acylphosphatidylethanolamine phospholipase D links dietary fat to metabolic adaptations in obesity and steatosis. *Nat. Commun.* **10**, 457 (2019).
196. Geurts, L., Muccioli, G. G., Delzenne, N. M. & Cani, P. D. Chronic endocannabinoid system stimulation induces muscle macrophage and lipid accumulation in type 2 diabetic mice independently of metabolic endotoxaemia. *PLoS One* **8**, e55963 (2013).
197. Suriano, F. et al. Exploring the endocannabinoidome in genetically obese (ob/ob) and diabetic (db/db) mice: links with inflammation and gut microbiota. *Biochim. Biophys. Acta Mol. Cell Biol. Lipids* **1867**, 159056 (2022).
198. Manca, C. et al. Germ-free mice exhibit profound gut microbiota-dependent alterations of intestinal endocannabinoidome signaling. *J. Lipid Res.* **61**, 70–85 (2020).
199. Suriano, F. et al. A lipidomics- and transcriptomics-based analysis of the intestine of genetically obese (ob/ob) and diabetic (db/db) mice: links with inflammation and gut microbiota. *Cells* **12**, 411 (2023).
200. Cohen, L. J. et al. Commensal bacteria make GPCR ligands that mimic human signalling molecules. *Nature* **549**, 48–53 (2017).
201. Misheva, M., Johnson, J. & McCullagh, J. Role of oxylipins in the inflammatory-related diseases NAFLD, obesity, and type 2 diabetes. *Metabolites* **12**, 1238 (2022).
202. Avila-Roman, J. et al. Impact of gut microbiota on plasma oxylipins profile under healthy and obesogenic conditions. *Clin. Nutr.* **40**, 1475–1486 (2021).
203. Gurup, A. et al. Effect of acute exercise on 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME) levels in obese male adolescents. *Clin. Endocrinol.* **99**, 174–181 (2023).
204. Moens de Hase, E. et al. *Dysosmobacter welbionis* effects on glucose, lipid and energy metabolism are associated with specific bioactive lipids. *J. Lipid Res.* **64**, 100437 (2023).
205. Le Roy, T. et al. *Dysosmobacter welbionis* is a newly isolated human commensal bacterium preventing diet-induced obesity and metabolic disorders in mice. *Gut* **71**, 534–543 (2022).
206. Fernandez-Veledo, S. & Vendrell, J. Gut microbiota-derived succinate: friend or foe in human metabolic diseases? *Rev. Endocr. Metab. Disord.* **20**, 439–447 (2019).
207. Ariza, A. C., Deen, P. M. & Robben, J. H. The succinate receptor as a novel therapeutic target for oxidative and metabolic stress-related conditions. *Front. Endocrinol.* **3**, 22 (2012).
208. Louis, P. & Flint, H. J. Formation of propionate and butyrate by the human colonic microbiota. *Environ. Microbiol.* **19**, 29–41 (2017).
209. Wu, G. D. et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science* **334**, 105–108 (2011).
210. De Filippo, C. et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc. Natl Acad. Sci. USA* **107**, 14691–14696 (2010).
211. Chia, L. W. et al. Deciphering the trophic interaction between *Akkermansia muciniphila* and the butyrogenic gut commensal *Anaerostipes caccae* using a metatranscriptomic approach. *Antonie Van Leeuwenhoek* **111**, 859–873 (2018).
212. Cani, P. D., Depommier, C., Derrien, M., Everard, A. & de Vos, W. M. *Akkermansia muciniphila*: paradigm for next-generation beneficial microorganisms. *Nat. Rev. Gastroenterol. Hepatol.* **19**, 625–637 (2022).
213. Wang, K. et al. *Parabacteroides distasonis* alleviates obesity and metabolic dysfunctions via production of succinate and secondary bile acids. *Cell Rep.* **26**, 222–235.e5 (2019).
214. Sadagopan, N. et al. Circulating succinate is elevated in rodent models of hypertension and metabolic disease. *Am. J. Hypertens.* **20**, 1209–1215 (2007).
215. McCreath, K. J. et al. Targeted disruption of the SUCNR1 metabolic receptor leads to dichotomous effects on obesity. *Diabetes* **64**, 1154–1167 (2015).
216. Monfort-Ferre, D. et al. The gut microbiota metabolite succinate promotes adipose tissue browning in crohn's disease. *J. Crohns Colitis* **16**, 1571–1583 (2022).
217. Massier, L. et al. Adipose tissue derived bacteria are associated with inflammation in obesity and type 2 diabetes. *Gut* **69**, 1796–1806 (2020).
218. Anhê, F. F. et al. Type 2 diabetes influences bacterial tissue compartmentalisation in human obesity. *Nat. Metab.* **2**, 233–242 (2020).
219. Amar, J. et al. Involvement of tissue bacteria in the onset of diabetes in humans: evidence for a concept. *Diabetologia* **54**, 3055–3061 (2011).
220. de Goffau, M. C. et al. Recognizing the reagent microbiome. *Nat. Microbiol.* **3**, 851–853 (2018).
221. Church, D. L. et al. Performance and application of 16S rRNA gene cycle sequencing for routine identification of bacteria in the clinical microbiology laboratory. *Clin. Microbiol. Rev.* **33**, e00053-19 (2020).
222. Sun, J. et al. The visceral adipose tissue bacterial microbiota provides a signature of obesity based on inferred metagenomic functions. *Int. J. Obes.* **47**, 1008–1022 (2023).
223. Cinti, S. Pink adipocytes. *Trends Endocrinol. Metab.* **29**, 651–666 (2018).
224. Selma-Royo, M., Calvo Lerma, J., Cortes-Macias, E. & Collado, M. C. Human milk microbiome: from actual knowledge to future perspective. *Semin. Perinatol.* **45**, 151450 (2021).
225. Collado, M. C., Laitinen, K., Salminen, S. & Isolauri, E. Maternal weight and excessive weight gain during pregnancy modify the immunomodulatory potential of breast milk. *Pediatr. Res.* **72**, 77–85 (2012).
226. Fernandez, L. & Rodriguez, J. M. Human milk microbiota: origin and potential uses. *Nestle Nutr. Inst. Workshop Ser.* **94**, 75–85 (2020).
227. Fernandez, L., Pannaraj, P. S., Rautava, S. & Rodriguez, J. M. The microbiota of the human mammary ecosystem. *Front. Cell. Infect. Microbiol.* **10**, 586667 (2020).
228. Mohandas, S. & Pannaraj, P. S. Beyond the bacterial microbiome: virome of human milk and effects on the developing infant. *Nestle Nutr. Inst. Workshop Ser.* **94**, 86–93 (2020).
229. Cani, P. D. & Van Hul, M. Microbial signatures in metabolic tissues: a novel paradigm for obesity and diabetes? *Nat. Metab.* **2**, 211–212 (2020).
230. Bluher, S., Shah, S. & Mantzoros, C. S. Leptin deficiency: clinical implications and opportunities for therapeutic interventions. *J. Investig. Med.* **57**, 784–788 (2009).
231. Suleiman, J. B., Mohamed, M. & Bakar, A. B. A. A systematic review on different models of inducing obesity in animals: advantages and limitations. *J. Adv. Vet. Anim. Res.* **7**, 103–114 (2020).
232. Healey, G. R., Murphy, R., Brough, L., Butts, C. A. & Coad, J. Interindividual variability in gut microbiota and host response to dietary interventions. *Nutr. Rev.* **75**, 1059–1080 (2017).
233. Schlomann, B. H. & Parthasarathy, R. Timescales of gut microbiome dynamics. *Curr. Opin. Microbiol.* **50**, 56–63 (2019).
234. Cerdó, T., García-Santos, J. A., Bermúdez, M. G. & Campoy, C. The role of probiotics and prebiotics in the prevention and treatment of obesity. *Nutrients* **11**, 635 (2019).

235. Nearing, J. T., Comeau, A. M. & Langille, M. G. I. Identifying biases and their potential solutions in human microbiome studies. *Microbiome* **9**, 113 (2021).
236. Bharti, R. & Grimm, D. G. Current challenges and best-practice protocols for microbiome analysis. *Brief. Bioinform* **22**, 178–193 (2021).
237. Levitan, O. et al. The gut microbiome — does stool represent right? *Heliyon* **9**, e13602 (2023).
238. Chikina, A. & Matic Vignjevic, D. At the right time in the right place: how do luminal gradients position the microbiota along the gut? *Cell Dev.* **168**, 203712 (2021).
239. Zoetendal, E. G. et al. Mucosa-associated bacteria in the human gastrointestinal tract are uniformly distributed along the colon and differ from the community recovered from feces. *Appl. Env. Microbiol.* **68**, 3401–3407 (2002).
240. Vaga, S. et al. Compositional and functional differences of the mucosal microbiota along the intestine of healthy individuals. *Sci. Rep.* **10**, 14977 (2020).
241. Canfora, E. E., Meex, R. C. R., Venema, K. & Blaak, E. E. Gut microbial metabolites in obesity, NAFLD and T2DM. *Nat. Rev. Endocrinol.* **15**, 261–273 (2019).
242. Ranjan, R., Rani, A., Metwally, A., McGee, H. S. & Perkins, D. L. Analysis of the microbiome: advantages of whole genome shotgun versus 16S amplicon sequencing. *Biochem. Biophys. Res. Commun.* **469**, 967–977 (2016).
243. Sharpton, T. J. An introduction to the analysis of shotgun metagenomic data. *Front. Plant. Sci.* **5**, 209 (2014).
244. Van Hul, M. et al. From correlation to causality: the case of *Subdoligranulum*. *Gut Microbes* **12**, 1–13 (2020).
245. Chusyd, D. E., Wang, D., Huffman, D. M. & Nagy, T. R. Relationships between rodent white adipose fat pads and human white adipose fat depots. *Front. Nutr.* **3**, 10 (2016).
246. Borgeson, E., Boucher, J. & Hagberg, C. E. Of mice and men: pinpointing species differences in adipose tissue biology. *Front. Cell Dev. Biol.* **10**, 1003118 (2022).
247. Bagchi, D. P. & MacDougald, O. A. Identification and dissection of diverse mouse adipose depots. *J. Vis. Exp.* https://doi.org/10.3791/59499 (2019).
248. Vitali, A. et al. The adipose organ of obesity-prone C57BL/6J mice is composed of mixed white and brown adipocytes. *J. Lipid Res.* **53**, 619–629 (2012).
249. Cohen, C. A., Shea, A. A., Heffron, C. L., Schmelz, E. M. & Roberts, P. C. Intra-abdominal fat depots represent distinct immunomodulatory microenvironments: a murine model. *PLoS One* **8**, e66477 (2013).
250. Foster, M. T. et al. Transplantation of non-visceral fat to the visceral cavity improves glucose tolerance in mice: investigation of hepatic lipids and insulin sensitivity. *Diabetologia* **54**, 2890–2899 (2011).
251. Wueest, S., Yang, X., Liu, J., Schoenle, E. J. & Konrad, D. Inverse regulation of basal lipolysis in perigonadal and mesenteric fat depots in mice. *Am. J. Physiol. Endocrinol. Metab.* **302**, E153–160 (2012).
252. Stenkula, K. G. & Erlanson-Albertsson, C. Adipose cell size: importance in health and disease. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **315**, R284–R295 (2018).
253. Kowaltowski, A. J. Cold exposure and the metabolism of mice, men, and other wonderful creatures. *Physiology* **37**, 253–259 (2022).
254. Armani, A. et al. Nutraceuticals in brown adipose tissue activation. *Cells* **11**, 3996 (2022).
255. Choi, Y. & Yu, L. Natural bioactive compounds as potential browning agents in white adipose tissue. *Pharm. Res.* **38**, 549–567 (2021).
256. Reynes, B., Palou, M., Rodriguez, A. M. & Palou, A. Regulation of adaptive thermogenesis and browning by prebiotics and postbiotics. *Front. Physiol.* **9**, 1908 (2018).
257. Zhou, L., Xiao, X., Zhang, Q., Zheng, J. & Deng, M. Deciphering the anti-obesity benefits of resveratrol: the "gut microbiota-adipose tissue" axis. *Front. Endocrinol.* **10**, 413 (2019).
258. Hui, S. et al. Resveratrol enhances brown adipose tissue activity and white adipose tissue browning in part by regulating bile acid metabolism via gut microbiota remodeling. *Int. J. Obes.* **44**, 1678–1690 (2020).
259. Liao, W. et al. Resveratrol-induced white adipose tissue browning in obese mice by remodeling fecal microbiota. *Molecules* **23**, 3356 (2018).
260. Baskaran, P., Krishnan, V., Ren, J. & Thyagarajan, B. Capsaicin induces browning of white adipose tissue and counters obesity by activating TRPV1 channel-dependent mechanisms. *Br. J. Pharmacol.* **173**, 2369–2389 (2016).
261. Kida, R. et al. Direct action of capsaicin in brown adipogenesis and activation of brown adipocytes. *Cell Biochem. Funct.* **34**, 34–41 (2016).
262. Lee, S. G., Parks, J. S. & Kang, H. W. Quercetin, a functional compound of onion peel, remodels white adipocytes to brown-like adipocytes. *J. Nutr. Biochem.* **42**, 62–71 (2017).
263. Pei, Y. et al. Effect of quercetin on nonshivering thermogenesis of brown adipose tissue in high-fat diet-induced obese mice. *J. Nutr. Biochem.* **88**, 108532 (2021).
264. Sheng, L. et al. Obesity treatment by epigallocatechin-3-gallate-regulated bile acid signaling and its enriched *Akkermansia muciniphila*. *FASEB J.* **32**, 6371–6384 (2018).
265. Li, C. et al. Berberine ameliorates obesity by inducing GDF15 secretion by brown adipocytes. *Endocrinology* **164**, bqad035 (2023).
266. Xu, Y. et al. Berberine modulates deacetylation of PPARγ to promote adipose tissue remodeling and thermogenesis via AMPK/SIRT1 pathway. *Int. J. Biol. Sci.* **17**, 3173–3187 (2021).
267. Wu, L. et al. Berberine promotes the recruitment and activation of brown adipose tissue in mice and humans. *Cell Death Dis.* **10**, 468 (2019).
268. Regnier, M. et al. Rhubarb supplementation prevents diet-induced obesity and diabetes in association with increased *Akkermansia muciniphila* in mice. *Nutrients* **12**, 2932 (2020).
269. Regnier, M. et al. Inulin increases the beneficial effects of rhubarb supplementation on high-fat high-sugar diet-induced metabolic disorders in mice: impact on energy expenditure, brown adipose tissue activity, and microbiota. *Gut Microbes* **15**, 2178796 (2023).
270. Anhe, F. F. et al. Treatment with camu camu (*Myrciaria dubia*) prevents obesity by altering the gut microbiota and increasing energy expenditure in diet-induced obese mice. *Gut* **68**, 453–464 (2019).
271. Zheng, X. et al. Membrane protein Amuc_1100 derived from *Akkermansia muciniphila* facilitates lipolysis and browning via activating the AC3/PKA/HSL pathway. *Microbiol. Spectr.* **11**, e0432322 (2023).
272. Deng, L. et al. Diverse effects of different *Akkermansia muciniphila* genotypes on Brown adipose tissue inflammation and whitening in a high-fat-diet murine model. *Microb. Pathog.* **147**, 104353 (2020).
273. Depommier, C. et al. Pasteurized *Akkermansia muciniphila* increases whole-body energy expenditure and fecal energy excretion in diet-induced obese mice. *Gut Microbes* **11**, 1231–1245 (2020).
274. Dao, M. C. et al. *Akkermansia muciniphila* and improved metabolic health during a dietary intervention in obesity: relationship with gut microbiome richness and ecology. *Gut* **65**, 426–436 (2016).
275. Agus, A., Clement, K. & Sokol, H. Gut microbiota-derived metabolites as central regulators in metabolic disorders. *Gut* **70**, 1174–1182 (2020).
276. Scheja, L. & Heeren, J. The endocrine function of adipose tissues in health and cardiometabolic disease. *Nat. Rev. Endocrinol.* **15**, 507–524 (2019).
277. James, D. E., Stockli, J. & Birnbaum, M. J. The aetiology and molecular landscape of insulin resistance. *Nat. Rev. Mol. Cell Biol.* **22**, 751–771 (2021).
278. Morigny, P., Boucher, J., Arner, P. & Langin, D. Lipid and glucose metabolism in white adipocytes: pathways, dysfunction and therapeutics. *Nat. Rev. Endocrinol.* **17**, 276–295 (2021).
279. Clemente-Suarez, V. J. et al. The role of adipokines in health and disease. *Biomedicines* **11**, 1290 (2023).
280. Lazar, V. et al. Gut microbiota, host organism, and diet trialogue in diabetes and obesity. *Front. Nutr.* **6**, 21 (2019).
281. Jardon, K. M., Canfora, E. E., Goossens, G. H. & Blaak, E. E. Dietary macronutrients and the gut microbiome: a precision nutrition approach to improve cardiometabolic health. *Gut* **71**, 1214–1226 (2022).
282. Gerard, C. & Vidal, H. Impact of gut microbiota on host glycemic control. *Front. Endocrinol.* **10**, 29 (2019).

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Competing interests
P.D.C. is an inventor on patent applications dealing with the use of specific bacteria and components in the treatment of different diseases. P.D.C. was co-founder of The Akkermansia Company SA and Enterosys. M.V.H. declares no competing interests.

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