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Perspective

Host-microbial interactions in the metabolism of different dietary fats

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SUMMARY

Although generally presumed to be isocaloric, dietary fats can differ in their energetic contributions and metabolic effects. Here, we show how an explicit consideration of the gut microbiome and its interactions with human physiology can enrich our understanding of dietary fat metabolism. We outline how variable human metabolic responses to different dietary fats, such as altered ileal digestibility or bile acid production, have downstream effects on the gut microbiome that differentially promote energy gain and inflammation. By incorporating host-microbial interactions into energetic models of human nutrition, we can achieve greater insight into the underlying mechanisms of diet-driven metabolic disease.

INTRODUCTION

Fat is the most concentrated source of energy in the human diet (Holt, 1957; Merrill and Watt, 1955) and energy yields from fat have shaped the evolution of our species (Leonard et al., 2010; Speth, 2010). Prior to the industrial production of trans fats, there were three main types of fat in the human diet: saturated fats sourced from animal foods and certain nuts; monounsaturated fats from animal- and plant-based oils; and polyunsaturated fats, including essential omega(ω)-3 and ω-6 fatty acids (Figure 1). While different dietary fats represent branched carbon chains of varying length and with varying degrees of "unsaturation" through C-C double bonds, traditional Atwater-based metrics for caloric value assign approximately 9 kcal/g to all dietary fats regardless of lipid structure (Merrill and Watt, 1955). Although longer fatty acid chains contain more carbons, the weight of these lipid molecules is also greater, so they remain isocaloric when controlling for mass (Merten, 1970). This static assessment of caloric value has been supported by observations that a low fraction of ingested fat is excreted in feces regardless of fat type (Cummings et al., 1978; Kasper, 1970; Walker et al., 1973). Therefore, the prevalent assumption is that all fats are uniformly absorbed and contribute roughly equally to host energy gain.

This assumption demands more rigorous testing because different dietary fats have been associated with differential risks of metabolic disease (Nettleton et al., 2013). Incidence of metabolic disease is rising rapidly in industrialized and developing populations (Corbett et al., 2018). A key factor linked to this rise, along with reduced physical activity and other lifestyle changes, has been the habitual intake of diets with an increased level of food processing, more sugar, less fiber, and a greater proportion of calories from dietary fat, particularly saturated fatty acids from agricultural animal sources (Kearney, 2010). A breadth of knowledge exists regarding the impacts of dietary fat intake on metabolic disease (Duan et al., 2018; Harford et al., 2011; Ooi et al., 2015; Sacks et al., 2017; De Souza et al., 2005; Woods et al., 2004). Consumption of high-fat diets has been shown to correlate with impaired insulin sensitivity (De Souza et al., 2005), which contributes to the onset of obesity and type 2 diabetes (Harford et al., 2011). High fat intake is also associated with increased fat storage and hyperleptinemia (Woods et al., 2004), cardiovascular disease (Sacks et al., 2017), and both intestinal and systemic inflammation (Duan et al., 2018; Harford et al., 2011). Diets relatively rich in saturated fat and artificial trans fats have been repeatedly associated with these negative effects (Grossman, 2015; Micha and Mozaffarian, 2010; Nettleton et al., 2013; Pan et al., 2008; Wells, 2006); by contrast, monounsaturated and polyunsaturated fats are generally regarded as neutral or beneficial for metabolic health (Mensink and Katan, 1989; Oh et al., 2005; Willett et al., 1995) (Figure 1). Indeed, studies in which saturated fats are replaced isocalorically with monounsaturated or polyunsaturated fats have typically reported improved metabolic outcomes (Berglund et al., 2007; Hodson et al., 2001; Mozaffarian et al., 2010).

Canonical views of nutrition and human physiology do not adequately explain why differences in dietary fat type are linked to such varying effects on metabolic health, raising the possibility of important exogenous effects—including those of the gut microbiome, which includes the bacteria, archaea, eukaryotes, and viruses residing within the gastrointestinal tract (the gut microbiota) and their combined genomes, transcripts, and metabolites (Hutenhower et al., 2012; Ley et al., 2006a). Humans rely on the gut microbiome for a range of physiological processes, including priming and educating the immune system, metabolizing drugs and other xenobiotic compounds, and breaking down complex carbohydrates and other indigestible nutrients (Carmody et al., 2019; Lynch and Pedersen, 2016; Sonnenburg and Bäckhed, 2016; Spanogiannopoulos et al., 2016). Mounting evidence also suggests that the gut microbiome has a profound influence on energy metabolism.

The direct impacts of the gut microbiome on energy metabolism have been documented using fecal transplant studies. Dramatic increases in body fat have been observed within

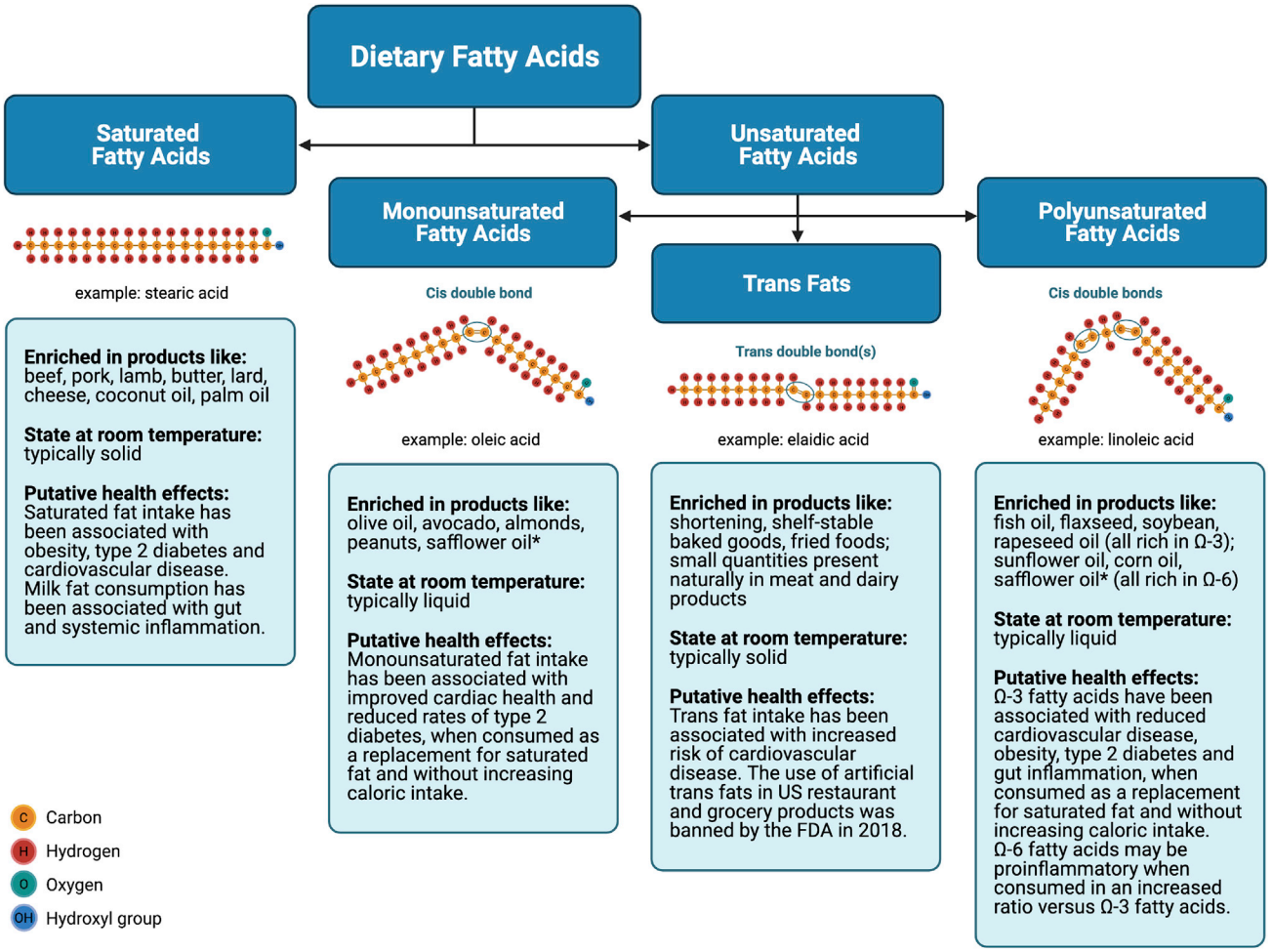

Figure 1. The main sources of fatty acids in the human diet and their putative health effects

Dietary fats are generally classified as "saturated" or "unsaturated" fatty acids. Saturated fatty acids are comprised of single-branched carbon chains with no double bonds; these fatty acid types are prevalent in terrestrial animal foods, as well as in plant foods such as coconut or palm oil. Unsaturated fatty acids contain either *cis* or *trans* double bonds along the carbon chain. Monounsaturated fats contain a single *cis* double bond, and are predominantly found in plant-based oils such as olive oil. Polyunsaturated fats contain multiple *cis* double bonds in their chemical structure, and are found in a range of vegetable oils, as well as seeds and fish. Trans fatty acids are a class of unsaturated fats that contain *trans* double bonds in their carbon structures. Trans fatty acids can be naturally sourced in small quantities in animal products, but are also artificially produced for commercial goods, although their commercial use has recently been banned by the United States Food and Drug Administration (Grossman, 2015). Saturated and trans fatty acids have been linked to negative effects on metabolic health, including systemic inflammation, cardiovascular disease, and obesity (Grossman, 2015; Micha and Mozaffarian, 2010; Nettleton et al., 2013; Pan et al., 2008; Wells, 2006). In contrast, polyunsaturated fatty acids are thought to confer positive health effects, particularly in the case of omega(ω)-3 fatty acids (Mensink and Katan, 1989; Oh et al., 2005; Willett et al., 1995). *Safflower oil can be sourced from two different plant varieties, one rich in oleic acid (a monounsaturated fat) and the other rich in linoleic acid (an ω-6 polyunsaturated fat).

2 weeks following inoculation of germ-free mice with a gut microbial community harvested from conventional mice, despite these recipients exhibiting lower energy intake and higher energy expenditure post-colonization (Bäckhed et al., 2004). Transitioning from germ-free to colonized status can be reliably expected to increase energy gain and adiposity, apart from rare exceptions such as the gut microbial communities associated with kwashiorkor (Smith et al., 2013) and after Roux-en-Y gastric bypass surgery (Liou et al., 2013).

Critically, different gut microbial communities can contribute differently to host energy balance (Bäckhed et al., 2004; Ley et al., 2006b; Ridaura et al., 2013; Turnbaugh and Gordon, 2009; Turnbaugh et al., 2008), as exemplified by studies in which murine recipients of a gut microbiome harvested from obese donors gain more body fat than recipients with lean donors (Ridaura et al., 2013; Turnbaugh et al., 2006). Gut microbial contributions to human metabolic health have also been inferred from the observation of a strong association between a particular phenotype, such as leanness, and the presence or abundance of specific microbial taxa, such as Christensenellaceae, that are then supported by human-to-mouse transplant studies establishing a causal effect (Goodrich et al., 2014). In addition, human-to-human fecal microbiota transplantation (FMT) has provided some evidence for amelioration of insulin insensitivity (Vrieze et al., 2012), although the effects on obesity remain unclear (Allegretti et al., 2021; Leong et al., 2020; Yu et al., 2020a). Certainly, methods of donor selection and screening still require refinement (Kelly et al., 2015), as illustrated by off-target effects of

FMTs witnessed even in closely related human donor-recipient pairs (Alang and Kelly, 2015).

Evidence in humans and mice suggests that the gut microbiome responds rapidly and reproducibly to dietary shifts, particularly when shifts involve differences in dietary fat intake (Carmody et al., 2015; David et al., 2014). Furthermore, the gut microbiome has been shown to play a causal role in a range of diet-induced metabolic disorders, including cardiovascular disease (Tang et al., 2013; Wang et al., 2015), obesity (Bäckhed et al., 2004; Cani et al., 2007; Ridaura et al., 2013; Turnbaugh et al., 2006), insulin resistance (Cani et al., 2007; Zeevi et al., 2015), and non-alcoholic fatty liver disease (Michail et al., 2015). The digestive partnership between humans and our resident gut microbes promotes a holobiont view of energy gain, which captures host and microbial mechanisms of energy harvest and their interactions (Zilber-Rosenberg and Rosenberg, 2008).

In this Perspective, we aim to advance the understanding of fat metabolism by considering the influence of dietary fat type on mammalian metabolic processes and their downstream effects on gut microbial response. We first provide an overview of mammalian mechanisms of fat digestion and absorption, and discuss how these processes may differ in response to different dietary fat types. Next, we consider the microbiome-driven pathways that may be involved in fat metabolism. In reviewing mammalian and microbial mechanisms of fat metabolism, we discover a range of host-microbial interactions implicated in energy gain that may play a role in differentiating the caloric value of fat. We therefore incorporate these interactions into a holobiont model of energy gain from dietary fats. However, many of these underlying mechanisms have been assessed in model systems, but not humans, and in some cases the available evidence only allows us to infer association rather than causation. We thus conclude by highlighting opportunities for future translational research.

HOST-DRIVEN FAT METABOLISM

Impacts of dietary fat type on metabolic health

Exogenous fats are necessary for a range of essential processes, including structuring of cell membranes (Murphy, 1990), protection of vital organs (Ballabriga, 1994), and general growth and development (Innis, 1991). The energetic contribution of dietary fats has been critical in fueling the evolution of the capacious human energy budget linked to increases in body size and relative brain size and habitually high daily activity expenditure throughout the lifespan (Carmody and Wrangham, 2009; Herculano-Houzel, 2012; Pontzer et al., 2016). The emergence of these traits has been linked to enhanced exploitation of high-quality foods with greater caloric density, especially items rich in fat (Carmody et al., 2011; Eaton, 1992; Speth, 2010; Wrangham et al., 1999).

Modern human diets source anywhere from 10% to 58% of daily energy from fats (Cordain, 2006; Cordain et al., 2002; Eaton, 1992; German and Dillard, 2004; Linseisen et al., 2009; Mennen et al., 2000), with reported saturated fat consumption ranging from as little as 3% to as high as 31% of calories across populations (Babio et al., 2012; Banini et al., 2003; Beegom and Singh, 1997; deGonzague et al., 1999; Galanis et al., 1999; Lyu et al., 1994; Ohno et al., 1997; Rodríguez-Morán et al., 2008). Saturated fats have been most often linked to cardiometabolic disease (Kratz et al., 2013; Micha and Mozaffarian, 2010), while the essential polyunsaturated fats that cannot be synthesized via *de novo* lipogenesis (Hulbert et al., 2014) do not appear to result in the same rates of chronic metabolic disease when consumed at commensurate levels (Buckley and Howe, 2009; Connor, 2000; Eritsland, 2000; Uusitupa et al., 1994). However, the canonical view that saturated fat is "bad" and polyunsaturated fats are "good" for health is not as clear-cut as once believed. For instance, different polyunsaturated fatty acids may themselves vary in their consequences for health (Figure 1).

The typical "Western" diet has a ratio of nearly 4:1 ω-6 to ω-3 fat intake, which can be attributed to the development of processed vegetable oils by the food industry (Dunbar et al., 2014). A high ω-6 to ω-3 fatty acid ratio has been argued to contribute to a range of chronic inflammatory diseases, including inflammatory bowel disease, cardiovascular disease, and obesity (Patterson et al., 2012). Nevertheless, co-occurrence of different fatty acids in any given food source complicates these studies, and it is possible that health issues may relate instead to low ω-3 fats rather than high ω-6 or saturated fats in industrial food products (Simopoulos, 2008). While numerous health recommendations have focused on different fat types (Aranceta and Pérez-Rodrigo, 2012; Krauss et al., 1996; Smit et al., 2009), our current understanding of nutrition lacks concrete mechanistic explanations for why some dietary fats may contribute more than others to metabolic disease.

Ketogenic diets illustrate how a simple appraisal of calories from fat does not translate easily into energy gain. The ketogenic diet, which recommends boosting fat intake in order to restrict carbohydrate intake to 5%–10% of total calories (Freeman et al., 2006), has risen in popularity in recent years. Although dietary fat routinely comprises 70%–80% of total caloric intake on a ketogenic diet, short-term ketogenic interventions in humans have resulted in weight loss (Paoli, 2014; Westman et al., 2008), a result attributable to carbohydrate deprivation leading to ketone production via fat oxidation (Freeman et al., 2006). Moreover, epileptic children prescribed a ketogenic diet to minimize seizures do not appear to exhibit increased metabolic disease under calorie-restricted conditions (Kossoff and Rho, 2009). Emerging evidence supports the possibility that the gut microbiome may be involved in the metabolic effects of a ketogenic diet. In both humans and mice, *ad libitum* consumption of ketogenic diets (comprised of at least 80% fat) resulted in distinct gut microbial signatures compared to either low-fat or traditional high-fat diets, with ketone bodies selectively reducing the relative abundance of bifidobacteria (Ang et al., 2020). Interestingly, increased plasma concentration of host-derived ketone bodies led to gut microbial shifts in a dose-response manner, and these shifts in turn led to reduced intestinal pro-inflammatory Th17 cells (Ang et al., 2020). This heightened production of ketone bodies is not sustained in mice consuming traditional high-fat diets that do not involve carbohydrate deprivation (Sunny et al., 2010). The effects of a ketogenic diet underscore that the metabolic consequences of fat intake can depend on context and interactions with the gut microbiome.

Factors beyond increased and differential intake of dietary fats are certainly involved in the etiology of metabolic disease, including a shift to a more sedentary lifestyle (Lieberman, 2015; Sparling et al., 2000) and a rise in simple carbohydrate

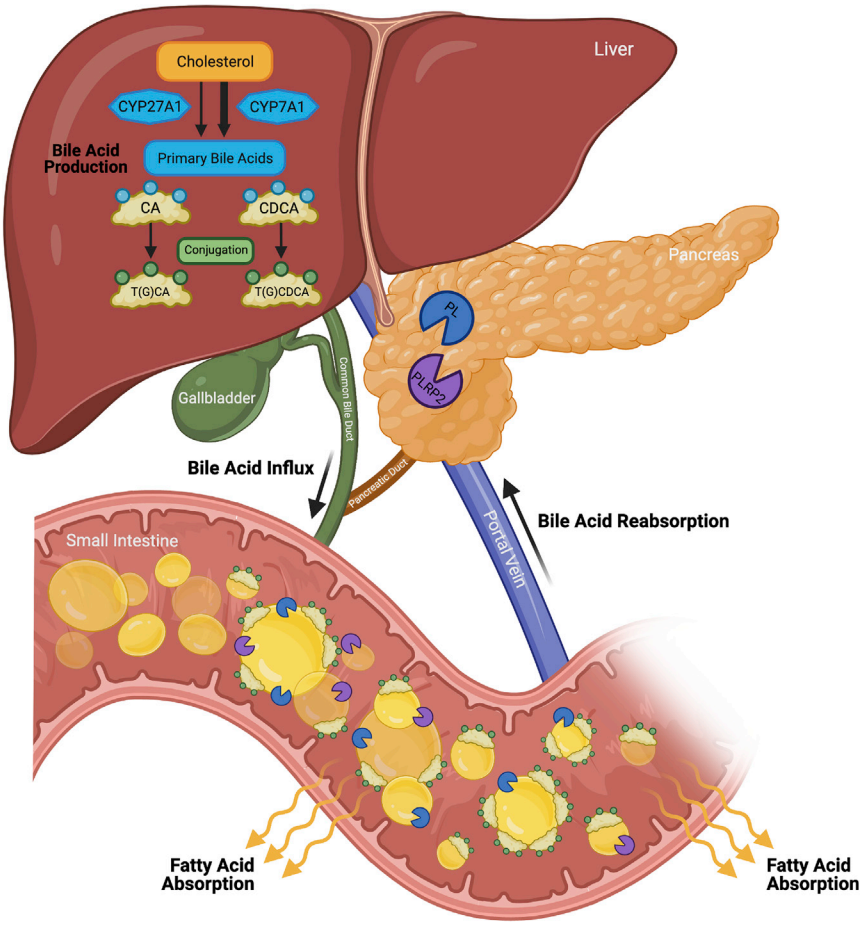

Figure 2. Overview of fat metabolism in the small intestine

Primary bile acids are synthesized from cholesterol in the liver and are stored in the gallbladder. During fat digestion, primary bile acids flow into the small intestine via the common bile duct. Cholic acid (CA) and chenodeoxycholic acid (CDCA) are the main primary bile acids produced in humans. Cytochrome P450 7A1 (CYP7A1) and cytochrome P450 27A1 (CYP27A1) are the enzymatic drivers of CA and CDCA production (Hofmann and Small, 1967; Ridlon et al., 2014; de Aguiar Vallim et al., 2013; Wahlström et al., 2017). Primary bile acids can also undergo conjugation in the liver, which transforms CA into either taurocholic acid (TCA) or glycocholic acid (GCA), and CDCA into either taurochenodeoxycholic acid (TCDCA) or glycochenodeoxycholic acid (GCDCA). During emulsification and absorption, two main pancreatic lipases in humans, pancreatic lipase (PL) and pancreatic lipase related protein 2 (PLRP2), are produced in the pancreas and enter the small intestine through the pancreatic duct. These pancreatic lipases play a role in the breakdown of fat globules formed by long-chain fatty acids. Bile acid emulsification and lipase activity may be required to different degrees for different fatty acid sources.

consumption (Blaak and Saris, 1995; Clemens et al., 2016). Nevertheless, evidence for strong associations between metabolic health outcome and differences in the amount and/or profile of fat consumption imply that dietary fats should not be automatically treated as metabolically equivalent.

Small intestinal digestion and absorption of fats

Despite the essential role of dietary fat in human physiology, we currently lack a robust understanding of how dietary fats differ in their absorption kinetics, or in their downstream consequences for energy gain and other metabolic phenotypes. The process of mammalian lipid metabolism occurs in five steps in the small intestine: (1) emulsification, in which hydrophobic fat globules are broken into smaller droplets (micelles) through the action of bile acids; (2) hydrolysis, in which dietary triglycerides are digested by pancreatic lipase, producing free fatty acids and monoglycerides; (3) absorption, in which fatty acids and monoglycerides diffuse through the mucosal lining of the small intestine and into epithelial cells; (4) reassembly, in which free fatty acids and monoglycerides are recombined into triglycerides inside the endoplasmic reticulum of epithelial cells; and (5) transport, in which triglycerides are shielded with proteins, forming water-soluble chylomicrons that allow transport of lipids beyond the gut (Carey et al., 1983) (Figure 2). Whether dietary fats escape digestion in the small intestine is dependent on numerous factors, including the volume of fat ingested (Cummings et al., 1978; Kasper, 1970; Walker et al., 1973), the type of dietary fat (Andrews and Lewis, 1970; Duran-Montgé et al., 2007; Skřivan et al., 2018; Steele and Moore, 1968; Zollitsch et al., 1997), concurrent fiber and protein intake (Huhtanen et al., 2009; Jørgensen et al., 1992), and perhaps even the composition of the gut microbiota (Martinez-Guryn et al., 2018; Semova et al., 2012). In all cases, excretion is assumed to be the fate of dietary fats that pass into the colon, which lacks the capacity to absorb fats directly. Hence, dietary fats entering the colon are assumed not to confer any caloric value to the host.

Up to 98% of ingested and endogenous lipids are thought to be absorbed in the small intestine, with different fat types exhibiting similar rates of fecal excretion at comparable levels of intake in humans (Cummings et al., 1978; Kasper, 1970; Walker et al., 1973) (Figure 2). Nevertheless, empirical data suggest that the absorption of different dietary fats throughout the gastrointestinal tract is not fixed. For instance, studies of healthy humans consuming different levels of dietary fat found that higher fat intake resulted in higher fecal fat and bile acid excretion when controlling for caloric intake (Cummings et al., 1978; Walker et al., 1973). The length of fatty acid chains also impacts digestion and absorption, with shorter carbon chains exhibiting more complete absorption by the terminal ileum (Ramírez et al., 2001) and faster rates of gastric emptying (Hunt and Knox, 1968) compared to longer chains. Moreover, evidence in agricultural animals indicates that ileal digestibility differs by fat type, with long-chain saturated fatty acids showing the lowest rates of absorption (Andrews and Lewis, 1970; Duran-Montgé et al., 2007; Skřivan et al., 2018; Steele and Moore, 1968; Zollitsch et al., 1997). For example, ileal digestibility was inversely correlated

with dietary long-chain saturated fatty acid content in pigs administered barley base diets supplemented with 10% fat derived from a range of fatty acid types (Duran-Montgé et al., 2007). In addition, stearic acid (c-18 saturated fatty acid) exhibited low ileal digestibility across all diet treatments in broiler chickens fed diets supplemented with either 6% lard, palm oil, or rapeseed oil (Skřivan et al., 2018). Notably, work in ruminants, which are generally thought to be efficient fat metabolizers, has also shown slightly lower ileal digestibility of saturated fats with greater carbon chain lengths (Andrews and Lewis, 1970; Steele and Moore, 1968). Despite these findings, further investigation is needed to determine whether dietary fat type is also likely to influence ileal digestibility in humans, particularly under high-fat conditions.

The role of bile acids in fat absorption

Efficient emulsification of dietary fats by bile acids is a key determinant of lipid digestibility (Bauer et al., 2005; Carey et al., 1983). In mammals, primary bile acids are produced in the liver through two enzymatic pathways (de Aguiar Vallim et al., 2013). The primary pathway, responsible for about 75% of total bile acid production in humans, depends on the presence of the enzyme cytochrome P450 7A1 (CYP7A1) to produce cholic acid (CA) and chenodeoxycholic acid (CDCA) (Hofmann and Small, 1967; Ridlon et al., 2014; de Aguiar Vallim et al., 2013; Wahlström et al., 2017) (Figure 2). A secondary pathway relies on the enzyme cytochrome P450 27A1 (CYP27A1), with its principal contribution thought to be in the form of CDCA synthesis (de Aguiar Vallim et al., 2013) (Figure 2).

Interestingly, it has been suggested that primary bile acids may only be necessary for the breakdown and absorption of long-chain saturated fatty acids with carbon chain lengths of c-16 or greater (Hofmann and Hagey, 2014; Lucassen, 1966), which are prevalent in domesticated meat and dairy products. Correspondingly, administration of the bile acid sequestrant cholestyramine to rats led to selective malabsorption of long-chain saturated fats (Harkins et al., 1965). Saturated fats were also absorbed at a lower rate than unsaturated fats in patients with short-bowel syndrome, a disorder causing a decrease in bile acid production (Heydorn et al., 1999). Upon supplementation of exogenous primary bile acids, patients exhibited reduced fat excretion that was especially pronounced for long-chain saturated fats, suggesting that primary bile acids were disproportionately important for long-chain saturated fat absorption (Heydorn et al., 1999). Furthermore, *in vitro* studies using everted gut sacs found that reduced bile acid concentrations resulted in lower esterification of palmitic acid (a saturated fat) versus linoleic acid (a ω-6 polyunsaturated fat) (Ockner et al., 1972), again suggesting that saturated fats may depend more on bile acids for efficient absorption than do unsaturated fats.

Of course, bile acids represent only one component of bile, with bile additionally containing a range of compounds such as bilirubin, phospholipids, cholesterol, amino acids, vitamins, and conjugated metabolites destined for excretion (Wheeler, 1972). Studies of digestive physiology have linked variations in dietary fat consumption to variations in bile composition and flow rate. Rats fed saturated fat diets exhibited an increase in circulating bile phospholipids and a decrease in bile flow rate compared to those fed polyunsaturated fat diets (Boquillon et al., 1979). Furthermore, administration of polyunsaturated fat in rats resulted in faster bile flow as well as higher concentrations of excreted biliary phospholipids and cholesterol when compared to monounsaturated fat (Paul and Ganguly, 1976). The effects of these broader bile dynamics on fat metabolism remain unknown, but presumably could influence fat digestibility, the rate and profile of bile acid synthesis, and the fraction of bile acids escaping reabsorption in the ileum.

Together, the available evidence suggests room for variation in the rate at which different dietary fats are emulsified and absorbed, with the digestibility of saturated fats appearing especially dependent on bile acid production. If saturated fats escape digestion to different extents (Andrews and Lewis, 1970; Duran-Montgé et al., 2007; Skřivan et al., 2018; Steele and Moore, 1968; Zollitsch et al., 1997) and/or require heightened bile acid activity for efficient digestion (Harkins et al., 1965; Heydorn et al., 1999; Ockner et al., 1972), achieving a better understanding of fat metabolism will require interrogation of mechanisms relevant to the colon and its extraordinarily dense, diverse, and variable microbiota.

MICROBIAL CONTRIBUTIONS TO FAT METABOLISM

The gut microbiome and its contributions to human metabolism are shaped by genetic factors (Goodrich et al., 2014; Gupta et al., 2017). For example, Christensenellaceae, a heritable microbial family in humans, is strongly associated with lean body mass (Beaumont et al., 2016; Goodrich et al., 2014; Tavella et al., 2021; Waters and Ley, 2019). However, the human gut microbiota appears to undergo the most significant shifts in response to environmental factors, especially diet (David et al., 2014; Rothschild et al., 2018). While human gut microbial signatures are more distinct and also more stable in response to dietary change than is the case in mice (Carmody et al., 2019; Johnson et al., 2019; Wu et al., 2011), dietary interventions in humans have reported a shared directionality of microbiota compositional shifts across individuals (Ang et al., 2020; Carmody et al., 2019; David et al., 2014; Mardinoglu et al., 2018; Turnbaugh et al., 2009) and convergence of microbial function (Ang et al., 2020; David et al., 2014) in response to shared dietary treatments. This notable effect of diet on the gut microbiome makes sense ecologically, as ingested substrates and their digestibility exert profound effects on the resources available in the colon (Carmody et al., 2019; Reese and Carmody, 2019; Sonnenburg et al., 2016). These diet-induced changes in the gut microbiome may contribute not only to energy gain, but to the overall metabolic state of the host (Carmody et al., 2019; Jumpertz et al., 2011; Murphy et al., 2010; Zmora et al., 2019).

Microbial interactions with dietary fat

The consumption of a high-fat diet has been shown to consistently alter gut microbial structure and function in mice, rats, and humans (David et al., 2014; Lecomte et al., 2015; Turnbaugh et al., 2006, 2008, 2009), with the resulting microbiota promoting enhanced energy harvest upon transplantation into gnotobiotic mice (Turnbaugh et al., 2006, 2009). Furthermore, high-fat-diet-induced changes in the gut microbiota have been shown to promote inflammation in the host (Belkaid and Hand, 2014;

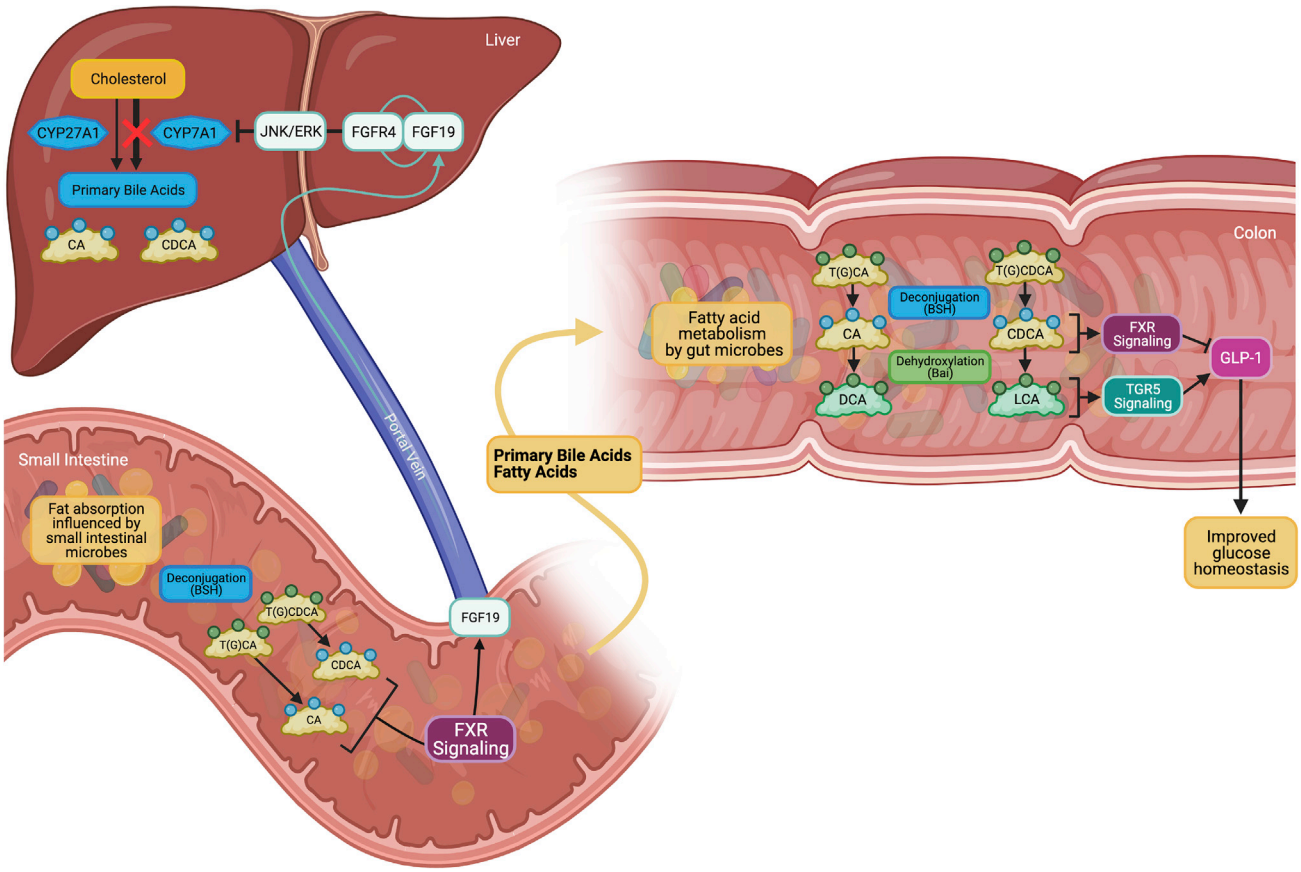

Figure 3. Microbial influences on fat metabolism

In the small intestine, jejunal microbes have been shown to influence fat digestion and absorption (Martinez-Guryn et al., 2018). Unabsorbed fatty acids and primary bile acids entering the colon provide substrates for microbial metabolism. Microbial mechanisms for mediating the antimicrobial effects of bile acid in humans include (1) deconjugation and dehydroxylation of primary bile acids, and (2) inhibition of primary bile acid production via farnesoid X receptor (FXR) signaling through a fibroblast growth factor 19 (FGF19)-mediated pathway (Ridlon et al., 2014; Wahlström et al., 2017). Certain gut microbes can exhibit bile salt hydrolase (BSH) activity, which leads to deconjugation of the bile acids taurocholic acid (TCA) or glycocholic acid (GCA) into cholic acid (CA), and taurochenodeoxycholic acid (TCDCA) or glycochenodeoxycholic acid (GCDCA) into chenodeoxycholic acid (CDCA). Microbes harboring bile acid inducible (*bai*) genes can then dehydroxylate unconjugated bile acids to form the secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA). Microbially deconjugated bile acids have been shown to activate FXR signaling in the ileum (Wahlström et al., 2016) and colon (Trabelsi et al., 2015). FXR increases expression of intestinal FGF19 in humans, which can travel via the portal vein and bind to fibroblast growth factor receptor 4 (FGFR4) in the liver to form a heterodimer complex. This heterodimer initiates a signaling cascade, involving c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinase (ERK), which leads to cytochrome P450 7A1 (CYP7A1) inhibition. Microbial dehydroxylation of bile acids in the colon leads to activation of G protein-coupled bile acid receptor 1 (TGR5) (Duboc et al., 2014; Wahlström et al., 2016), which activates glucagon-like peptide-1 (GLP-1) and can therefore improve glucose homeostasis (Pathak et al., 2018; Thomas et al., 2009). GLP-1 can also be inhibited by FXR activation in the colon (Trabelsi et al., 2015).

Dalal and Chang, 2014), suggesting the possibility of indirect inflammation-mediated effects on energy gain.

The effects of high-fat diets on the gut microbiome have frequently been attributed to the proportionately lower levels of dietary complex carbohydrates, which limits the fermentable substrates reaching the colon and therefore the energy available for colonic microbes (Sonnenburg and Bäckhed, 2016; Sonnenburg and Sonnenburg, 2014). The assumption that fat is not a microbially accessible energy source stems from the canonical view that dietary fat absorption in the small intestine is highly efficient. However, even slight changes in small intestinal absorption could have biologically meaningful effects on the gut microbiome and its influence on metabolic health (Carmody et al., 2019; Wilck et al., 2017), as the introduction of undigested fatty acids and/or primary bile acids into the colon would be expected to alter competition among gut microbes bearing different sensitivities and metabolic potentials. Differences in dietary fat composition likely also shape microbial communities in the small intestine, which have previously been shown to be sensitive to dietary fat intake (Martinez-Guryn et al., 2018) and to enhance fat absorption by the host (Martinez-Guryn et al., 2018; Semova et al., 2012) (Figure 3).

One mechanism by which gut microbes may indirectly affect fat metabolism is through intestinal signaling via short-chain fatty acids (SCFAs) and lactate. Lactate and SCFAs such as butyrate, acetate, and propionate, which are produced via gut microbial fermentation of complex carbohydrates, act as both energy sources and signaling molecules for the host (Donohoe et al., 2011; Koh et al., 2016). SCFA and lactate production have been shown to decrease intestinal inflammation in mice by downregulating pro-inflammatory responses in epithelial cells (Iraporda et al., 2015). Butyrate, which acts as the primary energy

source for colonocytes (Donohoe et al., 2011), has also been associated with greater insulin sensitivity in humans using microbiome-wide association studies (Sanna et al., 2019). Interestingly, signaling by microbial fermentation products has been shown in mice to differentially regulate fatty acid metabolism by enterocytes (Araújo et al., 2020). The production of L-lactate by the commensal microbe *Lactobacillus paracasei* promoted increased lipid storage in enterocytes through its conversion to malonyl-CoA, with resulting inhibition of carnitine palmitoyltransferase 1 (CPT-1) and fatty acid oxidation (Araújo et al., 2020). In contrast, acetate production by *Escherichia coli* led to increased fatty acid oxidation in mice via upregulation of the AMPK/PGC-1α/PPARα pathway (Araújo et al., 2020). These findings suggest that gut microbes may impact enterocyte function and fatty acid absorption in a diet-dependent manner.

Despite a large body of literature investigating gut microbial contributions to metabolic outcomes under high- versus low-fat conditions, there has been less exploration of effects mediated by different dietary fat types. In a systematic review of human studies, saturated fat intake was found to correlate with reduced gut microbial richness and diversity, as well as increased BMI (Wolters et al., 2019). Studies in mice have also shown that saturated fat intake leads to greater body mass than ω-3 polyunsaturated fat intake with concomitant changes in gut microbial community structure and function (Caesar et al., 2015; Huang et al., 2013). These data encourage further inquiry into gut microbiota-dependent mechanisms of energy gain from dietary fat.

Microbial interactions with bile acids

Recent research indicates that bile acids are capable of performing multiple functions. In addition to their role as emulsifiers, primary bile acids possess potent antimicrobial properties, which likely evolved in part to help the host suppress competition for nutrients in the small intestine (Walter and Ley, 2011). Primary bile acid production may therefore promote changes in the gut microbiome, with diverse downstream effects for host metabolism (Devkota and Chang, 2015; Devlin and Fischbach, 2015; Sagar et al., 2015) (Figure 3).

Although 90%–95% of the primary bile acid pool is reabsorbed in the ileum, the remaining 5%–10% can reach low millimolar concentrations in the colon (Adhikari et al., 2020; Bernstein et al., 1999). Colonic microbes can respond to primary bile acid exposure by converting primary bile acids into secondary forms (Figure 3). Conversion of primary to secondary bile acids by the colonic microbiota typically involves the removal of the 7α-hydroxy or 7β-hydroxy group, a process that can blunt the general antimicrobial properties of primary bile acids and instead confer narrow-spectrum antimicrobial activities targeting microbial competitors (Kang et al., 2019; Ridlon et al., 2006, 2016). Microbial taxa vary in their sensitivities and responses to bile acids (Ridlon et al., 2014, 2016; Wahlström et al., 2017), which suggests that differences in bile acid production across dietary fat levels (Hofmann, 1963) and types (Hofmann and Hagey, 2014) could directly shape the gut microbiome. For example, increased concentrations of the primary bile acid CA via supplemented feeding in rats has been shown to reduce gut microbial diversity and to increase the ratio of bacteria from the Firmicutes versus Bacteroidetes phyla (Islam et al., 2011), profiles that have previously been associated with increased microbial contributions to host energy harvest (Jumpertz et al., 2011; Turnbaugh and Gordon, 2009), although the causal effects of these microbial signatures remain unclear. In addition, variable conversion of primary to secondary bile acids may also have direct consequences for health, as increased levels of secondary bile acids in the colon have been linked to local pathology, including irritable bowel syndrome and colon cancer (Dior et al., 2016; Mower et al., 1979).

In a striking example of gut microbial manipulation of host physiology, gut microbes may also respond to primary bile acids through direct inhibition of host bile acid synthesis (Wahlström et al., 2016). Gut microbes can directly inhibit CYP7A1 in humans via upregulation of farnesoid X receptor (FXR) signaling through a fibroblast growth factor 19 (FGF19)-mediated pathway (Ridlon et al., 2014; Wahlström et al., 2017) (Figure 3). Upregulation of FXR signaling by members of the gut microbiota reduces bile acid concentrations in the gut, and consequently promotes increased levels of microbial colonization (Ridlon et al., 2014). While FXR is most highly expressed in ileal tissue, FXR receptors are found along the length of the gastrointestinal tract, including the colon (Cariou and Staels, 2006; Ding et al., 2015; Sivaprakasam et al., 2017; Yu et al., 2020b). Furthermore, production of FGF19 has been reported in both healthy and malignant human colonocytes (Calderon et al., 2020; Wang et al., 2019). Because the FXR signaling pathway is activated by microbially deconjugated bile acids in the colon (Trabelsi et al., 2015), it is possible that colonic microbes may contribute to FXR-mediated inhibition of CYP7A1. However, the process of microbially mediated CYP7A1 inhibition is not yet completely understood, and it is uncertain which microbial taxa are responsible for upregulating the FXR signaling pathway.

Bile acid transformations by the gut microbiota have also been linked to positive metabolic phenotypes. Microbial dehydroxylation of the primary bile acids CA and CDCA produces the secondary bile acids deoxycholic acid (DCA) and lithocholic acid (LCA), respectively, which are known to activate G protein-coupled bile acid receptor 1 (TGR5) (Duboc et al., 2014; Wahlström et al., 2016) (Figure 3). TGR5 activation increases glucagon-like peptide-1 (GLP-1) production by colonic L cells, which has been shown to improve glucose homeostasis in mice by upregulating mitochondrial oxidative phosphorylation and increasing the ratio of intracellular ATP/ADP, thereby enhancing intracellular calcium mobilization and insulin sensitivity (Pathak et al., 2018; Thomas et al., 2009) (Figure 3). In contrast, FXR signaling in the colon has been linked to the inhibition of GLP-1 in mice (Trabelsi et al., 2015) (Figure 3), indicating the likelihood that alternative strategies for bile acid manipulation by microbes may differentially impact human metabolic outcomes. Studies in mice further suggest that secondary bile acids may also activate TGR5 to induce metabolic responses in other tissues, including browning of white adipose tissue (Pathak et al., 2018), increased energy expenditure in brown adipose tissue (Thomas et al., 2009), and increased insulin production by pancreatic β cells (Kumar et al., 2012). Further investigation of gut microbial influences on bile acid production and composition may provide a link between different dietary fat types and broader gut microbial contributions to energy metabolism.

Relationships between dietary fat type, the gut microbiome, and metabolic health

The gut microbiome directly contributes to host inflammation and metabolic disease arising from high-fat diets (Bäckhed et al., 2004; Cani et al., 2007; Mars et al., 2020; Michail et al., 2015; Tang et al., 2013; Turnbaugh et al., 2006; Wang et al., 2015; Zeevi et al., 2015). For instance, high-fat diets have been associated with low-grade systemic inflammation via increases in circulating microbially derived lipopolysaccharides (LPSs) (Cani et al., 2007). LPSs are responsible for the activation of Toll-like receptors (TLRs) and downstream production of inflammatory cytokines in intestinal, adipose, liver, and other tissues (Cani et al., 2007; Hersoug et al., 2018; Shen et al., 2014; Triantafilou and Triantafilou, 2002). Activation of this signaling cascade correlates with intestinal inflammation in humans with inflammatory bowel disease (IBD) (Lu et al., 2018), as well as with obesity and insulin insensitivity in mice (Cani et al., 2007). In addition, high-fat diets have been linked to atherosclerosis through the microbial production of trimethylamine (TMA) from L-carnitine and phosphatidylcholine, which are found in fat-rich foods such as red meat and dairy products (Wang et al., 2015). TMA is then converted via hepatic flavin-containing monooxygenases to trimethylamine N-oxide (TMAO), a metabolite that has been causally linked to thrombosis in mice (Wang et al., 2015) and associated with major adverse cardiac events in humans (Tang et al., 2013).

Although less well studied, available evidence supports the possibility that exchanges in dietary fat type may similarly modulate host-microbial interactions in energy gain and inflammation. Mice fed a high-fat lard (rich in saturated fat) diet showed significantly greater weight gain compared with mice fed fish oil (rich in polyunsaturated fat), as well as a microbial profile—including enrichment of the genera *Bilophila*, *Bacteroides*, and *Turicibacter*—that promoted increased TLR4-activation of white adipose tissue (WAT) inflammation and insulin insensitivity (Caesar et al., 2015). Mice consuming the fish oil diet were protected from TLR-mediated inflammation, a phenotype that correlated with enrichment of the gut microbial genera *Akkermansia* and *Lactobacillus* (Caesar et al., 2015). Notably, inoculation of germ-free mice with microbiota conditioned on the fish oil diet reduced the inflammatory effects of lard diet feeding (Caesar et al., 2015), suggesting a direct role of the gut microbiota in mediating differential inflammation arising from different dietary fat types. These results support earlier findings that mice fed a high-fat diet containing palm oil (rich in saturated fat) exhibited an increased proportion of Firmicutes versus Bacteroidetes, as well as increases in body mass, liver triglyceride content, and insulin insensitivity compared with those fed olive oil (rich in monounsaturated fat) or safflower oil (rich in polyunsaturated fat) (de Wit et al., 2012). In contrast, consumption of soybean oil (rich in polyunsaturated fat) was found to promote obesogenic and diabetogenic phenotypes in mice compared to consumption of coconut oil (rich in long-chain saturated fat) (Deol et al., 2015). However, the soybean oil diet in this study derived 21% of calories from soybean oil and 19% from coconut oil (Deol et al., 2015), complicating the interpretation of the results.

Different dietary fat types may induce differential intestinal and chronic inflammation as a consequence of their variable effects on microbiota-driven bile acid recycling. Supporting this idea, intestinal inflammation has been linked to diets high in saturated fat (Kennedy et al., 2009), high-fat-diet-induced shifts in the gut microbial community (Belkaid and Hand, 2014; Caesar et al., 2015; Turnbaugh et al., 2009), and diet-derived emulsifiers (Chassaing et al., 2015; Lecomte et al., 2016). Inflammation arising from diets rich in saturated fat has previously been attributed to gut microbial responses to primary bile acids. Consumption of milk fat diets (rich in saturated fat) promoted colitis in *Il10*$^{-/-}$ mice compared to safflower oil diets (rich in polyunsaturated fat) (Devkota et al., 2012). This diet-induced colitis was attributable to increased concentrations of taurocholic acid, a primary conjugated bile acid also present in humans, that elicited blooms of the gut pathobiont *Bilophila wadsworthia* (Devkota et al., 2012). However, *Il10*$^{-/-}$ mice are genetically predisposed to gut inflammation, so further work is needed to determine whether the same effect of fat type occurs in healthy hosts.

While the mechanisms linking dietary fat type to chronic inflammation remain unclear, one potential mechanism could involve the emulsifying properties of bile acids reaching the colon. Intestinal inflammation, which may be promoted by diets rich in saturated fat as noted above, has been linked to malabsorption of bile acids in the small intestine (Lenicek et al., 2011), resulting in greater concentrations of primary bile acids in the colon. Ingestion of physiologically relevant concentrations of the common synthetic dietary emulsifiers carboxymethylcellulose and polysorbate-80 compromised the integrity of the mucosal lining of the small intestine, leading to bacterial encroachment toward the epithelium, inflammation, and metabolic syndrome in *Il10*$^{-/-}$ mice (Chassaing et al., 2015). Natural emulsifiers derived from soybean polar lipids also resulted in a rise in inflammation and metabolic syndrome in conventional mice (Lecomte et al., 2016). Notably, germ-free mice were protected from these outcomes (Chassaing et al., 2015), suggesting that host inflammatory and metabolic phenotypes are driven by increased contact with gut microbes and their products. Such data raise the intriguing but still untested hypothesis that endogenous emulsifiers such as bile acids could similarly contribute to inflammation and metabolic syndrome through their effects on the gut mucosal barrier and its interaction with the gut microbiome.

INSIGHTS FROM A HOLOBIONT VIEW OF ENERGY GAIN FROM FATS

Due to the highly digestible nature of fats (Carey et al., 1983), the process of fat metabolism has traditionally been modeled without significant consideration of the gut microbiome. Our review of host and microbial metabolic processes suggests numerous potential mechanisms by which the effective caloric value of dietary fats could be differentiated as a result of host-microbial interactions.

In our view, variations in either the consumption of different fat types or the total level of dietary fat can be expected to first induce changes in host-driven fat metabolism. For example, an increase in saturated versus polyunsaturated fat intake could drive decreased rates of intestinal absorption, due to the lower ileal digestibility of saturated fatty acids (Andrews and Lewis, 1970; Duran-Montgé et al., 2007; Skřivan et al., 2018; Steele and Moore, 1968; Zollitsch et al., 1997), and/or drive increased bile acid production, due to the increased reliance of long-chain

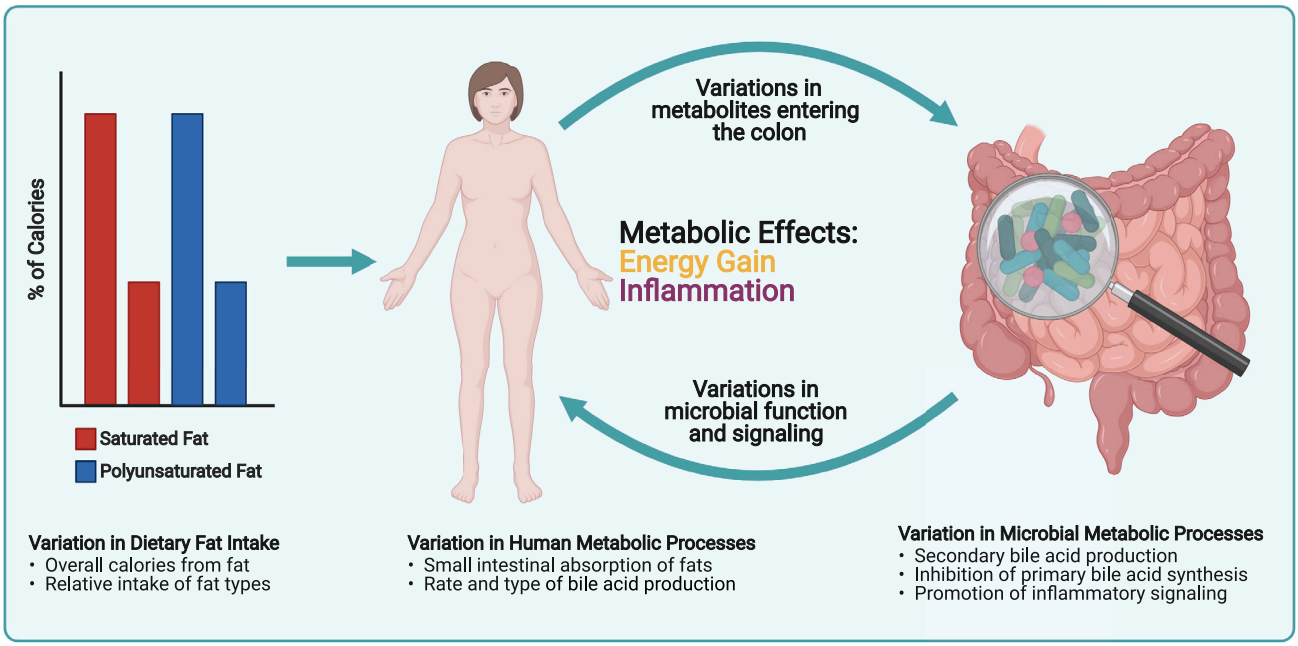

Figure 4. A holobiont framework of energy gain from dietary fats

There are a range of human-microbial interactions involved in fat metabolism that may work together on the scale of the holobiont to differentiate the metabolic effects of fat type. In this system, we use the example of diets rich in saturated versus polyunsaturated fat, and that vary in the level of fat intake. Variations in the type and/or level of dietary fat may induce variations in human-driven metabolic processes of fat digestion, including altered small intestinal absorption or differential production of primary bile acids. These responses in the host may affect the metabolites traveling downstream into the colon, which then induce structural and/or functional changes in the gut microbiome. An altered gut microbiome may in turn influence host phenotypes related to energy gain or inflammation.

saturated fats on bile acids for emulsification (Hofmann and Hagey, 2014; Lucassen, 1966). Such changes could be expected to modify the compounds entering the colon and interacting with resident gut microbes (Figure 4). In such cases, the gut microbiome may respond through compositional or functional changes (Figure 4). For example, colonic influx of fatty acids may advantage Firmicutes over Bacteroidetes (Lobionda et al., 2019; Turnbaugh et al., 2009). Increased primary bile acid concentrations may also increase the relative abundance of bile acid-tolerant taxa (Devkota et al., 2012; Zheng et al., 2017). Such gut microbial community shifts may then impact host energy metabolism in multiple ways, including via altered energy harvest (Turnbaugh et al., 2006), altered energy storage (Bäckhed et al., 2004), interactions with host-driven processes of fat digestion such as FXR signaling (Wahlström et al., 2017), and/or interactions with the immune system that promote inflammation (Caesar et al., 2015) (Figure 4). Evaluating the energetic significance of these mechanisms could lead to meaningful progress in understanding the metabolic consequences of dietary fat intake and why individuals harboring distinct microbial communities may experience variable outcomes on a given diet (Kant, 2004).

Testing the impacts of fat type on host-microbial interactions

Here, we offer a simplified framework that could be used to evaluate how host-microbial interactions differ with saturated versus polyunsaturated fat consumption, using calorie- and macronutrient-matched diets that vary only in fat type.

An important empirical step will be understanding the role of fat type on host-driven fat metabolism in the small intestine. Mechanistically, this could be assessed by feeding animal models different high-fat-diet treatments and measuring host metabolic processes related to fat emulsification and/or absorption. Based on findings that the emulsification of long-chain saturated fats requires greater bile acid activity (Harkins et al., 1965; Heydorn et al., 1999; Hofmann and Hagey, 2014; Lucassen, 1966), changes in overall production of primary bile acids or their composition may especially affect emulsification, and therefore absorption, of saturated fats. This process may occur through increased host expression of bile acid synthesis genes *CYP7A1* and *CYP27A1* in the liver and result in increased quantities or concentrations of bile entering the small intestine during fat digestion. It is possible that digestion of fat globules comprised predominantly of solid saturated fat might also alter the lipolytic activity of enzymes such as pancreatic lipase (PL) and pancreatic lipase-related protein 2 (PLRP2) at high concentrations (Ricketts and Brannon, 1994), or influence fat absorption through changes in smooth muscle activity and transit time (Ordway et al., 1991). Testing these metrics of emulsification and absorption would provide more clarity on host digestive processes that differ by fat type.

Our model also raises several questions regarding the effects of dietary fat type on the gut microbiome. In the case of high-fat diets comprised of different fat sources, variable levels of fatty acids and/or primary bile acids entering both the small intestine and the colon could be expected to shape competition among microbes bearing different metabolic potentials. Evidence also

suggests that host-driven processes of fat digestion may become less efficient as dietary fat levels increase, and that there may even be a threshold for intestinal lipid absorption (Cummings et al., 1978; Kasper, 1970; Walker et al., 1973). Under such circumstances, unabsorbed fats flowing into the colon may be directly metabolized by gut taxa such as *Clostridium* or *Turicibacter*, which are enriched in the jejunum under high-fat feeding conditions (Martinez-Guryn et al., 2018), possibly because they have functional advantages in accessing this resource. Furthermore, increased bile acid production by the host under conditions of high saturated fat intake may result in a greater influx of primary bile acids into the colon, thus enriching for bile acid-tolerant taxa in the families Ruminococcaceae and Lachnospiraceae, as well as the genera *Bacteroides* and *Bilophila*, that have previously been associated with host inflammation (Caesar et al., 2015; Devkota et al., 2012; Lobionda et al., 2019; Vital et al., 2019). Controlled feeding experiments that track longitudinal changes in the structure and function of the gut microbiome can be used to disentangle these possible mechanisms.

Finally, gnotobiotic experiments have shown that conditioning the microbiome on a high-fat diet can amplify host energy harvest and inflammation (Caesar et al., 2015; Ridaura et al., 2013; Turnbaugh et al., 2006). Whether conditioning the microbiome on different dietary fat sources has similar potential to alter host phenotypes remains unclear. To disentangle potential diet-microbiome-host interactions driven by dietary fat type, we recommend fully factorial gnotobiotic experiments in which recipients of murine and human gut microbial communities conditioned on different fat types receive all combinations of original donor diets. This experimental design can be used to determine the extent to which the metabolic effects of dietary fat type are attributable to the microbiome, whether there are substantial differences in the effects conferred by murine versus human communities, as well as whether these phenotypic changes are dependent on or amplified by continued exposure to the same type of dietary fat.

Elucidating host and microbial mechanisms that drive differential energy gain from dietary fats will benefit from dietary interventions conducted under conditions of strict genetic and environmental control, coupled to intensive fecal and tissue sampling, which often necessitates the use of animal models. Moreover, establishing causal effects of a diet-conditioned microbiome on host physiology will likely require gut microbiota transplants into antibiotic-treated or germ-free hosts. To date, such controlled experiments in mice have dominated investigations of host-microbial interactions. However, it must be noted that mice and humans differ in important aspects of digestion and metabolism. Unlike humans, mice have a rapid life history strategy (Promislow and Harvey, 1990), which reduces their reliance on dietary fat for growth and development (Clarke et al., 1977). Mice and humans also exhibit genomic differences that may differentiate their physiological responses to dietary fats. For instance, mice synthesize a different range of primary bile acids compared to humans (Takahashi et al., 2016), which may result in divergent emulsifying or signaling properties. One such bile acid, tauro-β-muricholic acid, has been shown to play a functional role in FXR inhibition in mice (Sayin et al., 2013), but is not produced in humans. Such species-specific functional responses may lead to discoveries using mouse models that are not translatable to humans (Lai et al., 2014). On the other hand, laboratory mice may be better physiological models than phylogeny alone would suggest, given that laboratory mice have been selectively bred to thrive in human environments and on human foods for over 150 generations (Beck et al., 2000), and that the gut microbiotas of laboratory mice and humans in industrialized populations exhibit unique similarities (Reese et al., 2021).

Ultimately, complementary studies in humans will be required to validate the translational potential of phenotypes and mechanisms established in animal models. Investigating correlations between reported macronutrient composition, dietary fat type, gut microbial structure, plasma metabolites and biomarkers, and overall metabolic phenotype can be done using large-scale interventional or prospective cohort studies that collect longitudinal stool samples from participants, such as PREDICT 1 (Asnicar et al., 2021) or the Nurses' Health Study II (Sinha et al., 2018), respectively. Crossover (within-subjects) dietary interventions are expected to provide the clearest insight because such studies enable accountancy for the substantial degree of interindividual variation in the human gut microbiome.

CONCLUSION

Given that the gut microbiota contributes substantially to energy gain, that different microbial communities exhibit differential contributions to energy gain, and that the gut microbiota shifts in response to dietary fat, comprehensive study of energy gain from dietary fat requires consideration of host-microbial interactions. We have challenged the idea that all fat types are metabolized similarly based on prior observations of differential dependence of dietary fats on bile acid-mediated absorption, gut microbial sensitivity to dietary fat type, as well as gut microbial influence on host-driven fat absorption and bile acid production. We thus argue that, even in the case of dietary fats, widely thought to be highly and invariably digestible, there is value in adopting an ecosystem perspective in the assessment of energetic value. By probing the impacts of dietary fat type on the holobiont, we can develop a better understanding of how human-microbial interactions contribute to diet-associated metabolic diseases on the rise in many parts of the world, and to variable outcomes observed in different individuals consuming similar diets. Discovering the dynamics between humans and our microbial co-residents in response to different dietary fats could reveal some of the unique features of human biology, and get us closer to appreciating the fundamental nature of the human-microbial partnership.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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