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Opinion paper

Towards microbiome-informed dietary recommendations for promoting metabolic and mental health: Opinion papers of the MyNewGut project

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SUMMARY

The gut microbiota coexists in partnership with the human host through adaptations to environmental and physiological changes that help maintain dynamic homeostatic healthy states. Break-down of this delicate balance under sustained exposure to stressors (e.g. unhealthy diets) can, however, contribute to the onset of disease. Diet is a key modifiable environmental factor that modulates the gut microbiota and its metabolic capacities that, in turn, could impact human physiology. On this basis, the diet and the gut microbiota could act as synergistic forces that provide resilience against disease or that speed the progress from health to disease states. Associations between unhealthy dietary patterns, non-communicable diseases and intestinal dysbiosis can be explained by this hypothesis. Translational studies showing that dietary-induced alterations in microbial communities recapitulate some of the pathological features of the original host further support this notion. In this introductory paper by the European project MyNewGut, we briefly summarize the investigations conducted to better understand

Abbreviations: DGAC, Dietary Guidelines Advisory Committee; EECs, enteroendocrine cells; EFSA, European Food Safety Authority; FFAR2, free fatty acid receptor 2; FFAR3, free fatty acid receptor 3; FGF, fibroblast growth factor; GABA, Gamma-Aminobutyric acid; GLP-1, glucagon like peptide-1; HDAC, histone deacetylase; NCDs, non-communicable diseases; PUFAs, polyunsaturated fatty acids; PYY, peptide YY; SCFAs, short-chain fatty acids; Treg, regulatory T cells; USDA, United States Department of Agriculture.

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the role of dietary patterns and food components in metabolic and mental health and the specificities of the microbiome-mediating mechanisms. We also discuss how advances in the understanding of the microbiome's role in dietary health effects can help to provide acceptable scientific grounds on which to base dietary advice for promoting healthy living.

1. Introduction

Gut microbiota is at the interphase between the inner and outer worlds. It interacts with the human host to orchestrate an array of bodily functions and moderates the impact of environmental exposure (diet, stress, medication, etc.) on human physiology. The partnership existing between the microbiota and the human host relies on two interrelated features. Firstly, it is specific to individuals and resilient to external threats (unhealthy diets, antibiotics, etc.), thus conferring temporal stability and reducing vulnerability to disease. Secondly, it is relatively flexible to common physiological and environmental changes (e.g. nutrient availability during lactation, immune development, etc.) through fluctuations within different healthy states ("dynamic equilibrium") to maintain homeostasis [1]. Breach of this delicate balance when faced with sustained or extreme exposure (e.g. infections, malnutrition) can, however, lead to profound ecological disruptions (dysbiosis) and a breakdown in the human-microbiome partnership. This has emerged as one of the complex mechanisms mediating the progression from health to disease.

For generations, unhealthy dietary patterns and a sedentary lifestyle have become major contributors to the increased prevalence of non-communicable diseases (NCDs), particularly of obesity and other cardiometabolic disorders [2,3]. Emerging evidence suggests that dietary habits, high-sugar and saturated-fat, also contribute to anxiety and mood disorders, which show bi-directional associations with obesity [4]. Diet is, on the other hand, one of the key environmental factors shaping the flexible fraction of our gut microbiota and its functions [5]. This can explain both associations between intestinal dysbiosis and cardiometabolic as well as anxiety and mood disorders [6,7] and some of the adverse dietary effects on the pathophysiology of these NCDs, particularly in the long-term. Most studies indicate that dietary-induced alterations in microbial communities recapitulate some of the pathological features of the original host, when the microbiota of the diseased individual is transferred to a new recipient, in both metabolic and mood disorders [6,8]. This evidence supports the role played by the dysbiotic microbiota in these alterations, regardless the sequence of events (i.e. whether dysbiosis is a cause or a secondary consequence of unhealthy diets and the associated disease). Observational and intervention studies show that Westernized diets, high in fat and low in fiber, reduce species diversity, cause a loss of bacteria specialized in fiber fermentation, and increase gut exposure to pro-inflammatory and carcinogenic metabolites in humans [9,10]. Changes from a rural to a Western diet also result in remarkable reciprocal changes in mucosal biomarkers of cancer risk, supporting the hypothesis that gut microbiota–diet interactions influence vulnerability to disease [9]. Experimental study models corroborate this evidence and demonstrate that these alterations can be transmitted through several generations, and partially restored by the re-introduction of dietary fiber [11]. From these findings, one can conclude that the dietary disease risk for developing NCDs is partly mediated by the microbiota configuration maintained by our dietary habits. Conversely, ancestral diets, rich in plant-based foods and fiber, seem to favor ecological diversity where bacterial species specialized in the metabolism of undigested nutrients (fibers, phytochemicals) are able to thrive and maintain a key core of protective microbial functions and host-microbe co-metabolic processes. This biochemical activity contributes to the generation of up to 50% of the metabolites of body fluids [12]. The generated metabolites are considered part of the microbial mechanisms that provide mucosal protection (i.e. short-chain fatty acids [SCFAs] such as butyrate) and connect the gut with other tissues and organs, including the brain, impacting their physiological functions [13]. Therefore, the relative plasticity of our gut microbiota also makes diet a tool able to reverse dysbiotic states and restore the host-microbe metabolic network to recover the dynamic "healthy state". Furthermore, diet could also be instrumental in disease prevention through its role in maintaining the human-microbiome partnership.

2. Today's dietary recommendations

Evidence of the value of individual lifestyle decisions and habits, including diet, in maintaining health and preventing chronic disease highlights the need to enable informed decisions and consumer's engagement with their own healthcare. This information should be based on dietary guidelines and evidence–based nutritional recommendations provided by national and international institutions and scientific advisory boards [14]. These are ultimately translated into legislative and policy programs (e.g. labelling), professional guidelines and messages for consumers, guiding them in their daily choices, regarding which foods and eating patterns contribute to their health status. This is of particular relevance in the struggle against obesity and comorbid conditions, where poor progress has been made in reducing prevalence rates. In this context, individual behavioral changes make up the key elements to effectively face a globalized food environment that, generally, reinforces preferences for palatable and energy dense foods [15].

Many studies demonstrate that dysbiosis is associated with unhealthy diets and NCDs, including obesity and more recently mood disorders [1,6,16]. These studies have indicated that disease can be linked to a number of microbiota features (reduced diversity, richness, etc.), candidate bacterial groups and, to a lesser extent, functional pathways. However, there are also inconsistencies in the results, due to the noise inherent to epidemiological studies, lack of minimal methodological standards and the scarcity of hypothesis-driven mechanistic studies done in parallel [17]. Furthermore, knowledge of how specific nutrients and foods could beneficially modify alterations in the microbiome profile is mostly based on small short-term intervention trials, which makes it difficult to draw definitive conclusions. Extra efforts are still needed to gain a better understanding of the microbiome components and functions causally related to a specific disease state, independently of regular temporal variations of the microbiome, and their possible restoration through specific dietary measures.

Our understanding of the microbiome's role in diet-mediated effects on health is still too limited to constitute evidence on which to base dietary recommendations. In fact, today's dietary guidelines and scientific opinions of authoritative bodies barely address the role of microbiome functionalities in human nutrition

and health. For example, in 2015 the United States Department of Agriculture (USDA) Scientific Report of Dietary Guidelines Advisory Committee [18] highlighted the interest in understanding how the microbial communities are influenced by diet, environment and host genetics, as well as their association with various health outcomes, but concluded that the existing evidence was insufficient to support dietary recommendations. Likewise, the European Food Safety Authority (EFSA) acknowledged the role of the gut microbiota in nutrition and health in only a few cases, like vitamin K production and fiber fermentation, which is considered a mechanism whereby gut microbes enhanced faecal bulk, contributing to regulating bowel habits [19]. Belgian dietary recommendations also mention that some fibers (such as pectins, gums, oligosaccharides and resistant starch) can be fermented by bacteria from the commensal microbiota and, therefore, cause physiological effects that are responsible for the promotion and/or maintenance of the bowel functions, such as lowering the pH in the intestine, ensuring balance of the microbiota and intestinal mobility [20]. Yet these and other functions (e.g. production of SCFAs that may influence systemic lipid and glucose metabolism) are not considered pillars of the body of evidence that base dietary recommendations.

The research community still has to make a concerted effort to support causal relationships between specific microbiota-mediated functions and health outcomes in order to constitute acceptable scientific grounds on which to base dietary advice.

3. The MyNewGut project

The FP7 EU project MyNewGut (www.mynewgut.eu) is a five-year initiative (2013–2018) integrated by a highly multidisciplinary team that cooperates to disentangle the role played by our gut microbiota, via interactions with lifestyle factors (e.g. diet, eating habits, stress, etc.), in the regulation of pathways leading to the development of obesity and the associated metabolic and behavioral disorders. With this purpose, the research team is conducting observational and intervention trials, targeting the microbiome (microbiota replacement, diet and ingredients), as well as parallel mechanistic studies in experimental models. In this way, we are approaching the question of causality between microbiome features and disease risk markers through interconnected translational studies. One of the ultimate goals of the MyNewGut consortium is to generate scientific knowledge that helps ground future microbiome-informed dietary recommendations, so they can constitute a tool promoting healthy lifestyles.

The specific objectives of the project are as follows:

- Identify specific components of the human gut microbiota and their metabolic pathways that are responsive to dietary intervention and contribute to nutrient metabolism, energy balance and disease risk.
- Identify microbiome-related features that contribute to and predict obesity and associated metabolic and behavioral disorders.
- Understand how the gut microbiota, under the influence of environmental factors, plays a role in programming the development and function of the metabolic, immune and nervous systems in early life and the long-term health consequences.
- Provide proof-of-concept of the potential of dietary interventions with innovative foods and ingredients, which target the gut microbiota, to reduce disease risk in humans.

Within this framework, the MyNewGut Consortium has recently worked on a set of Opinion Papers founded on the project results and the latest advances in the field. These reflect the progress made towards informing dietary habits and lifestyle from a wider perspective embracing the microbiome as an additional actor in the complex field of NCDs. The topics covered by the Opinion Papers are briefly addressed below.

4. Dietary impact on the inner world

Diet is a major instrument for modulating the structure and function of the human gut microbiota, as well as for altering the type and amount of bacterial metabolites and bacterial-host co-metabolic products, with a potential impact on metabolic and mental health. Dietary-induced shifts in microbiota composition constitute one of the mechanisms by which exposure to adverse bacterial components (e.g. endotoxin) could be reduced, thereby minimizing the risk of gut barrier disruption and immune deregulation [21]. A number of food-based bacterial-derived metabolites with potential effects on different aspects of human physiology are also identified. These include amino acid metabolites, organic acids including SCFAs, and secondary bile acids, which are thought to be responsible for some of the microbiota-mediated effects on the host metabolic phenotype and the interlinks with the immune and nervous systems [22].

Dietary proteins are first digested in the small intestine by human digestive enzymes, but about 10–12% reach the large intestine in a regular Western diet. This amount increases proportionally with the amount of dietary protein ingested in the context of high-protein diets. These diets increase satiety, favorably modify lipid metabolism, and facilitate weight management, but may also have deleterious effects on diverse tissues and organs, particularly in the long-term. The metabolic activity of the gut microbiota on protein-derived products, and especially on amino acids, generates numerous metabolites with suspected or established effects on host intestinal physiology, liver and peripheral tissues. Bacterial metabolites produced from protein fermentation include: hydrogen sulphide (H_2S), ammonia, aromatic compounds (phenol, p-cresol, indole), polyamines, SCFAs, branched-chain fatty acids (isobutyrate, 2-methylbutyrate), organic acids (formate, lactate, succinate), ethanol, gases (H_2, CO_2, CH_4), and compounds with potential neuroactive activity (gamma-aminobutyric acid [GABA], serotonin, histamine, L-DOPA, tryamine, nitric oxide, tryptamine, phenethylamine) among others [23]. The main roles of key metabolites resulting from microbial metabolism on nitrogenous compounds are schematized in Fig. 1.

The use of high-protein diets for weight management is widespread; however, we have yet to establish the maximum amount of protein that can be consumed without deleterious effects and to ascertain the beneficial or detrimental roles of different protein sources. To do so, we also need a better understanding of the biological role of microbial metabolites derived from different dietary proteins.

In this context, the paper by Blachier et al. entitled *"High-protein diets for weight management: Interactions with the intestinal microbiota and consequences for gut health"*, a position paper by the MyNewGut project, will focus on how dietary proteins influence the gut microbiota and the host-microbe co-metabolic processes and products. It will discuss the pros and cons of high-protein diets for body weight management and intestinal mucosal health. It will also discuss the effects of specific protein sources based on a double-blind randomized controlled trial conducted in MyNewGut. The new evidence generated in our project suggests the need to consider not only the amount of protein in the diet but also its quality in order to establish long-term dietary recommendations, particularly intended for weight management.

Dietary fiber is non-digested in the upper part of the intestinal tract and constitutes the main energy source for gut microbes. The beneficial effects of high-fiber diets on glucose and lipid metabolism and body weight management are well-established.

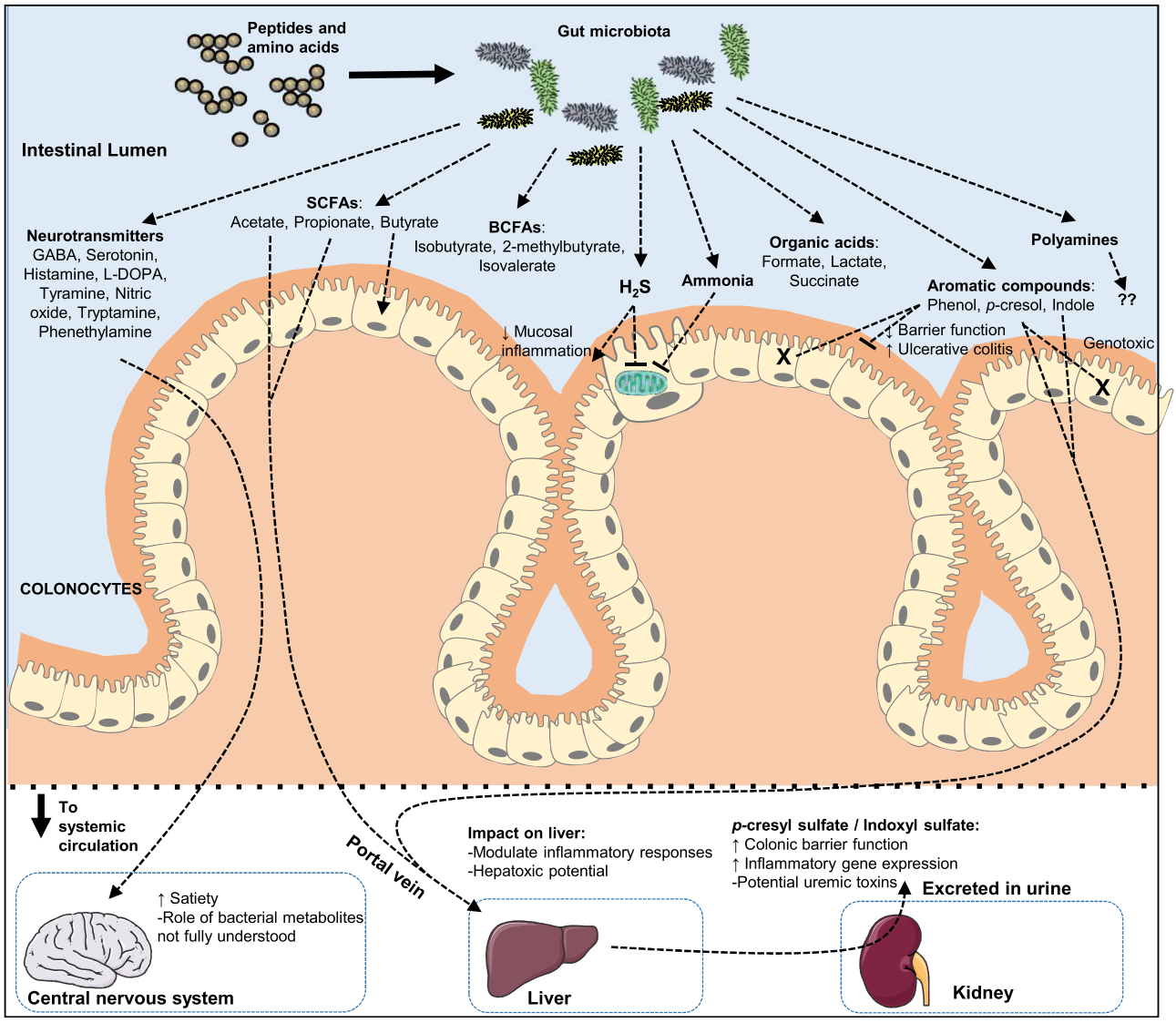

Fig. 1. Fate of dietary proteins and amino acids in the large intestine. As peptides and amino acids reach the colon, they are digested by the resident gut microbiota to smaller metabolites that can have direct positive or negative effects on the intestinal mucosal barrier and colonocytes. Alternatively, bacterial metabolites can travel via the portal vein to the liver where several tryptophan-derived metabolites have been shown to modulate inflammatory responses in hepatocytes, while tyrosine-derived metabolites like *p*-cresol have demonstrated hepatoxic potential. In the liver, fractions of the bacterial metabolite *p*-cresol can be conjugated to *p*-cresyl sulfate, which can travel to the kidneys where they can damage renal tubular cells. Another bacterial metabolite, indole, can undergo transformation in the liver to produce the uremic toxin indoxyl sulfate. Several metabolites can be excreted from the kidney, in which the majority of recovered urinary phenolic compounds consist of *p*-cresol. Bacterial metabolites from peptide hydrolisis and amino acid fermentation can influence immunity, hormone secretion from gut enteroendocrine cells and the nervous system. For instance, tryptophan metabolites (e.g. indole) play a role on immunity and inflammation and indole, tryptamine and tyramine could mediate effects of high protein diets on gut hormone secretion with an impact on satiety. The bacterial metabolites from amino acids also include neurotransmitters and their precursors, which could influence the enteric nervous system or enter the systemic circulation and reach the central nervous system. For example, serotonin not only modulate gastrointestinal motility but could also impact cognition, mood, appetite, etc. Additionally, neuronal excitability might be affected by microbiota-mediated production of GABA, an inhibitory neurotransmitter [5,23] (Illustrations are from Servier Medical Art).

Consumption of diets containing amounts of fiber above recommendations is associated with a reduced risk of coronary heart disease and type 2 diabetes. These beneficial effects of fibers are attributed to their physicochemical and structural properties (e.g. indigestibility, viscosity, etc.). The fermentative activity of gut microbiota on dietary fiber, on the one hand, increases the energy extracted from the diet, but also generates metabolites with presumed beneficial roles in energy metabolism as well as on ingestive and affective-emotional behavior [22,24]. The metabolites include organic acids (lactic, succinic acid) and SCFA (acetic, propionic and butyric acids). Although the effects and mechanisms of action of these metabolites are still not well understood, the knowledge about their possible physiological roles is summarized in Fig. 2.

The effects of dietary fibers largely vary depending on the amount and type of fiber and as a function of the individual [5]. The extent to which this modulation can be translated into physiological benefits in humans is still insufficient to provide specific recommendations based on microbiome-mediated effects. However, recent studies indicate that current dietary recommendations (25–30 g/day) could be below the consumption levels required for achieving some beneficial effects of fiber such as butyrogenesis [9].

A second position paper by Delzenne et al. entitled "*Nutritional interest of dietary fibers and prebiotics in obesity: lessons from the MyNewGut project*" will focus on the role of dietary fibers on gut microbiome functions that impact metabolic health, with an emphasis on those investigated in the MyNewGut project. This

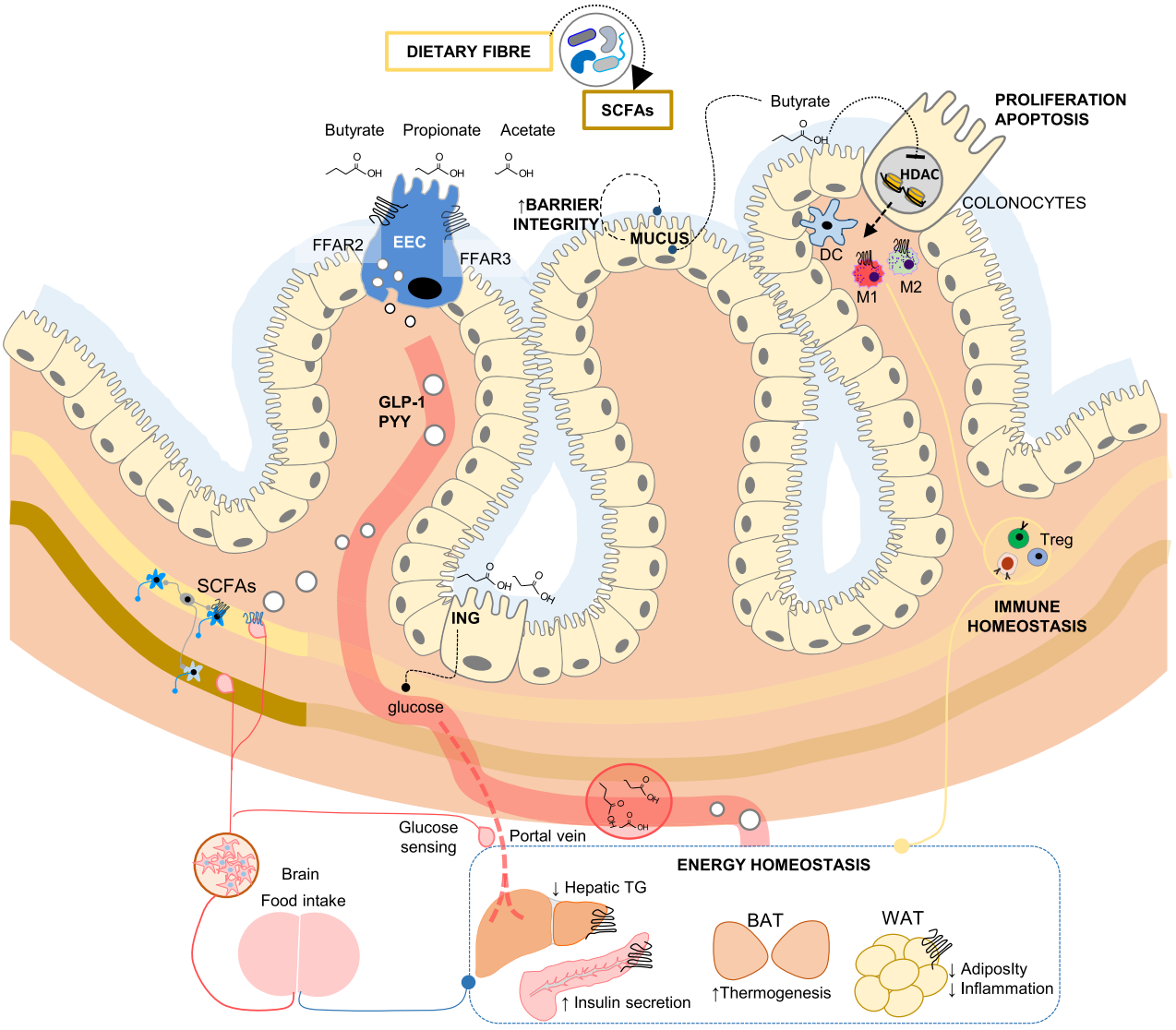

Fig. 2. Schematic representation of the main metabolites resulting from the activity of gut microbiota on dietary fiber and potential physiological roles. SCFAs (butyrate, propionate and acetate) are the main metabolic products derived from the fermentation of complex carbohydrates (fibers) by gut microbes. These metabolites are ligands of free fatty acid receptor (FFAR)2 and FFAR3 located in colonocytes, immune and enteroendocrine cells (EECs) and enteric neurons where they serve to trigger different biological actions. For instance, butyrate serves as an energy source for host colonocytes contributing to essential intestinal functions (i.e, proliferation, apoptosis and mucus production for the maintenance of gut barrier integrity). Intestinal immune homeostasis is maintained by diverse butyrate-mediated signalling mechanisms including inhibition of histone deacetylase (HDAC) in colonocytes, induction of functional colonic regulatory T cells (Treg) or polarization of M2 macrophages. Butyrate and propionate induce gluconeogenesis in intestinal epithelial cells (ING), a mechanism that transmits glucose sensing to the brain, which in turn modulates the central control of energy homeostasis. SCFAs binding to FFAR2/FFAR3 in EECs also regulate energy metabolism through the release of gut hormones (namely GLP-1 and peptide YY [PYY]) that induce endocrine effects in distal organs (e.g. liver, white or brown adipose tissue). In addition, SCFAs also impact intrinsic enteric neurons and autonomic intestinal innervations modulating the gut-brain communication which in turn affects the central control of energy homeostasis and feeding and/or emotional behavior. (Illustrations are from MOTIFOLIO).

research has ended with a more robust delineation of the exact fiber sources that beneficially impact specific components of the gut microbiota and metabolism and contribute to discovering new players and mechanisms of action that could support specific health-outcomes.

Dietary fat (amount and quality) is well-known to have an important influence on metabolism. Western diets rich in saturated fat are known to influence the structure of gut microbiota and its functions [25]. These effects could be due to reductions in other dietary components (e.g. carbohydrates) and also to the effects of fat

consumption on secretion and composition of the pool of bile acids. Primary bile acids are synthesized from cholesterol in the hepatocytes and circulate between the liver and intestine, where they are required for cholesterol solubilisation in the bile and dietary fat emulsification in the gut [26]. Synthesis is under the control of the nuclear Farnesoid X receptor (FXR) and its downstream targets fibroblast growth factor (FGF)15/19, activated by conversion of primary to secondary bile acids, which could reduce cholesterol levels. Once primary bile acids are secreted into the intestine, they are metabolized into secondary bile acids (deoxycholic and lithocholic acids) by the gut microbiota. Bile acids act as bactericidal compounds on the gut microbiota and as signalling molecules that regulate metabolism via activation of cell-receptors in the gut, liver and adipose tissue. Bile acids inhibit the growth of some microbiota components, while favoring the growth of others, such as the sulphite-reducing bacterium *Bilophila wadsworthia* that produces sulphide, which contributes to intestinal mucosa inflammation. Secondary bile acids also activate the G protein-coupled receptor TGR5 (TGR5) in enteroendocrine L-cells, inducing secretion of glucagon-like peptide-1 (GLP-1) and, thereby, improving liver and pancreatic function and enhancing glucose tolerance in mice [26]. Activation of TGR5 in brown adipose tissue and muscle also increases energy expenditure in mice [27]. Bile acid binding resins are shown to reduce serum cholesterol and improve glucose tolerance and insulin resistance in animal models and humans. In mice, resin administration activates both cholesterol and bile acid synthesis in liver and thermogenesis in brown adipose tissue [27].

The MyNewGut position paper by Wolters et al. entitled "*Dietary fat, the gut microbiota, and metabolic health - a systematic review*" will include a systematic review of current knowledge on the possible interactions of dietary fat including different types of fatty acids and, particularly, its relationship with gut microbiota, discussing their respective roles in the human metabolic phenotype. Concepts inspired by the results from MyNewGut intervention and observational studies related to obesity in children and metabolic risk markers will be included in the discussion.

Unhealthy dietary patterns are considered part of Westernized lifestyle changes that, together with other lifestyle factors (e.g. sedentary behavior), have contributed to the increased prevalence of behavioral and mood disorders [28,29]. The role of specific nutrients (e.g. polyunsaturated fatty acids [PUFAs], vitamins, minerals) in mental health is well-established and increasing evidence supports a role for dietary patterns in the risk of developing mental disorders, such as anxiety or depression [29,30]. In addition, associations between intestinal dysbiosis and mood disorders have recently been reported [31]. These findings support the notion that nutrition may impact mental health, partly through effects on the gut microbiota and its role in the gut-brain axis, which constitutes a new paradigm in neuroscience [31]. The paper by Dinan et al. entitled *"Feeding melancholic microbes: MyNewGut recommendations on diet and mood"* will provide an update on dietary patterns and components that could influence mood and emotions via regulation of the gut microbiota–brain axis. The paper by Campoy et al. "*Microbiome and early nutrition programming of neurodevelopment: new insights from the MyNewGut project*" will update our understanding of the role played by diet–microbiota interactions in different neurodevelopmental aspects, through the application of cutting-edge imaging technologies.

5. Microbiome imprinting confronts the one-size-fits-all approach

The dietary measures and interventions to combat NCDs should become more efficient by adopting strategies that consider the biological variables influencing the individual responses to dietary changes. This requires progress beyond the one-size-fits-all approach, traditionally applied to nutrition, and a move towards tailored dietary strategies. The high inter-individual variability of the microbiota is considered one of the factors underlying the different responses to diet. This could be partially explained by host-genome-microbiome associations reported recently [32]. So far, the microbiota configuration of the subject has been linked to their ability to lose weight [33] or their tendency to re-gain body weight after dietary intervention [34]. Likewise, it has been linked to the response of Irritable Bowel Syndrome patients to low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) diets [35]. Another study indicates that the glycemic responses to a specific food are better explained by integrating multiple personal variables, including the microbiome information (e.g. anthropometry, biochemistry, dietary intake, microbiome), in a mathematic algorithm [36]. Therefore, integration of microbiome information together with other person-specific factors appear to be essential to better understand the result of their complex interactions and predict dietary effects on health. This may help to reframe future dietary recommendations and improve their effectiveness, facilitating adherence to healthier lifestyles [14].

In MyNewGut, the role of the individual microbiota has also been investigated as a variable influencing the response to dietary interventions with fibers and PUFAs. These studies have revealed the existence of responders, non-responders and negative-responders. An intervention trial evaluating effects of fecal microbiota transplants on the gut-brain axis and the metabolic phenotype has also revealed a strong donor-effect, reinforcing the idea that the individual microbiota can impact metabolic outcomes. All in all, the findings suggest that subject stratification may be required to increase the effectiveness of interventions through microbiome-mediated mechanisms, progressing towards tailored interventions and personalized nutritional approaches.

6. Conclusions

Diet seems to be the most attainable approach to preventing chronic NCDs and promoting health in the long-term. Modulation of gut microbiome functionalities could be a key mediator of dietary effects on health. Therefore, experts within the MyNewGut consortium consider that future dietary recommendations should take into account how to meet, not only human nutritional requirements, but also those of the gut microbiota. In doing so, we will be able to promote the desired microbial ecosystem services for the human host and, thereby, maintain homeostatic control of healthy states. Subject stratification as a function of person-specific variables, including the microbiota, may also be required to increase the effectiveness of dietary interventions on health maintenance and disease risk management.

Author contribution

YS drafted the original manuscript. MRP and KP prepare the figures. All authors contributed to discussion, editing and approval of the final manuscript.

Conflict of interest

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